Clinical Case Reports

Open Access

CASE REPORT

Iron overload-related heart failure in a patient with transfusion-dependent myelodysplastic syndrome reversed by intensive combined chelation therapy

Valeria Pinto[1], Manuela Balocco[1], Ilaria Ambaglio[2], Giorgio Derchi[3], Luca Malcovati[2] & Gian Luca Forni[1]

[1]Ematologia-Centro della Microcitemia e Anemie Congenite, Ospedale Galliera, Genoa, Italy
[2]Department of Hematology Oncology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy
[3]Unità di Cardiologia, Ospedale Galliera, Genoa, Italy

Correspondence
Gian Luca Forni, Ematologia-Centro della Microcitemia e Anemie Congenite, Ospedale Galliera, Via Volta 6, 16128 Genoa, Italy.
Tel: +390105634557; Fax: +390105634556;
E-mail: gianluca.forni@galliera.it

Funding Information
No sources of funding were declared for this study.

Received: 13 July 2015; Revised: 2 September 2015; Accepted: 5 September 2015

Clinical Case Reports **2015; 3(11): 952–954**

doi: 10.1002/ccr3.407

Key Clinical Message

Patients with transfusion-dependent myelodysplastic syndromes (MDS) have an increased risk of cardiac events, due to both chronic anemia and iron overload. Here, we report the recovery of cardiac function after an intensive iron chelation therapy in a MDS patient who had developed heart failure due to iron overload.

Keywords

Deferiprone, desferal, heart failure, iron chelation, myelodysplastic syndromes.

The finding that intensive iron chelation therapy (ICT) can aid recovery of cardiac function in heart failure resulting from myocardial iron deposition in β-thalassemia major (TM), has dramatically decreased the number of deaths due this life-treating complication [1–3]. Patients with transfusion-dependent myelodysplastic syndromes (MDS) also have an increased risk of cardiac events, due to both chronic anemia and iron overload [4]. Here, we report the use of intensive ICT in a low-risk transfusion-dependent MDS patient with *SF3B1* mutations who had developed heart failure due to iron overload.

A 78-year-old man with refractory anemia with ring sideroblasts presented in our clinic. He carried a somatic mutation of *SF3B1* (K700E allelic burden 41.4%) [5, 6], and was H63D heterozygous for HFE gene.

Treatment with epoetin alfa (40,000 UI twice weekly) had been unsuccessful, so he was regularly transfused. After receiving 25 units of packed red blood cells (PRBC), the patient's serum ferritin value was 1214 μg/L and the magnetic resonance imaging (MRI) showed a mild liver iron overload with T2-star (T2*) of 4.1 msec $\pm$ 0.61 (liver T2* normal value >6.3 msec).

The patient was started on subcutaneous deferoxamine (DFO; 30 mg/kg/day five times per week) [7–9], but with limited compliance. After 4 months, the patient was switched to deferasirox (DFX; 15 mg/kg/day). Deferasirox was well tolerated initially, but later the patient experienced headache and systemic skin reactions affecting his legs. Chelation therapy was discontinued and when the patient was subsequently twice rechallenged at a lower dose of DFX plus a low dose of steroid, the skin reaction reappeared. During this time, the median serum ferritin increased to 1595 μg/L and the liver iron overload worsened, T2* by MRI was 2.16 msec $\pm$ 0.37.

By contrast, cardiac MRI indicated a myocardial T2* of 29 $\pm$ 4.23 msec (heart T2* normal value >20 msec) and a normal left ventricular ejection fraction (LVEF; 61%, normal value >55%). After twelve months of chelation therapy with DFX with a limited compliance, DFO was

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

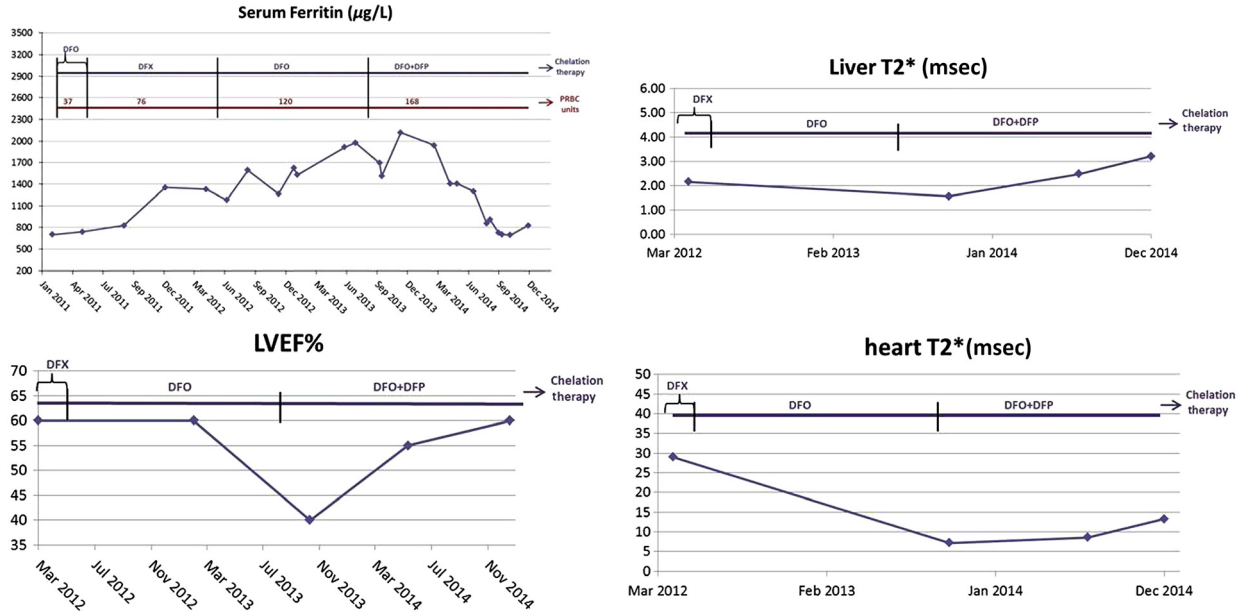

Figure 1. Patient trend of serum ferritin, liver T2*, LVEF , heart T2* with chelation and transfusion therapy.

restarted (at 40 mg/kg daily) but compliance was still low. After 15 months of chelation therapy with DFO, effort dyspnea appeared (NYHA class III) and transthoracic echocardiography showed a reduction in LVEF (to 40%). The serum ferritin value increased to 2118 μg/L, while the blood transfusion requirement was similar. Cardiac MRI indicated a myocardial T2* of 7.9 ± 1.33 msec (severe iron overload T2* < 10 msec) without alterations of delayed enhancement. Holter EkG recording was normal, and ergometric stress test and angioTC were negative. No endocrinopathies were pointed out.

Based on the reversal of cardiac disease obtained by the combined therapy with deferiprone (DFP) and DFO observed in TM patients – and after having obtained off-label consent from our Ethical Committee and written informed consent from the patient –combined ICT was prescribed. The patient received DFP at 50 mg/kg in three doses/day and then increased to 75 mg/Kg after 2 weeks, and DFO was received at 30 mg/kg daily. Hematological parameters were monitored weekly.

After 6 months of therapy, transthoracic echocardiography and MRI indicated a recovery in LVEF to 55%. During the first year of combined ICT, the patient experienced a stable improvement in both cardiac and hepatic condition, and the volume of blood products used remained stable. Median serum ferritin was 1186 μg/L and MRI evaluation showed cardiac T2* of 13.3 ± 1.37 msec and liver T2* 3.22 msec (Fig. 1). Iron overload is common in transfusion-dependent low-risk MDS patients. It was recently shown that *SF3B1* mutation is significantly associated with a high degree of ineffective erythropoiesis and marked suppression of hepcidin, resulting in increased iron absorption and recirculation. However, whether these changes may result in parenchymal iron overload and organ damage is still unclear.

After 120 PRBC units, the patient here reported developed a clinically significant liver and cardiac iron overload, suggesting that in MDS associated with *SF3B1* mutation, suppression of hepcidin mediated by ineffective erythropoiesis may result in a clinically relevant parenchymal iron overload [10].

Use of DFP is not widely used because of the risk of granulocytopenia [11]. The efficacy and safety of combined ICT in reducing severe IO is well-known in patients affected by TM [2], but to the best of our knowledge, this is the first report showing its use in a transfusion-dependent MDS patient. Our findings suggest that combined ICT with DFP and DFO should be used safely and effectively to restore cardiac function in patients with transfusion-dependent MDS experiencing heart failure due to iron overload.

Conflict of Interest

None declared.

References

1. Borgna-Pignatti, C., S. Rugolotto, P. De Stefano, H. Zhao, M. D. Cappellini, G. C. Del Vecchio, et al. 2004. Survival and complications in patients with thalassemia major

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

treated with transfusion and deferoxamine. Haematologica 89:1187–1193.
2. Lai, M. E., R. W. Grady, S. Vacquer, A. Pepe, M. P. Carta, P. Bina, et al. 2010. Increased survival and reversion of iron-induced cardiac disease in patients with thalassemia major receiving intensive combined chelation therapy as compared to desferoxamine alone. Blood Cells Mol. Dis. 45:136–139.
3. Modell, B., M. Khan, M. Darlison, M. A. Westwood, D. Ingram, D. J. Pennell. 2008. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J. Cardiovasc. Magn. Reson. 25:42.
4. Malcovati, L., M. G. Della Porta, C. Strupp, I. Ambaglio, A. Kuendgen, K. Nachtkamp, et al. 2011. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Haematologica 96:1433–1440.
5. Malcovati, L., E. Papaemmanuil, I. Ambaglio, C. Elena, A. Gallì, M. G. Della Porta, et al. 2014. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. Blood 124:1513–1521.
6. Ambaglio, I., L. Malcovati, E. Papaemmanuil, C. M. Laarakkers, M. G. Della Porta, and A. Gallì, et al. 2013. Inappropriately low hepcidin levels in Patients with myelodysplastic syndrome carrying a somatic mutation of SF3B1. Haematologica 98:420–423.
7. Malcovati, L., E. Hellstrom-Lindberg, D. Bowen, L. Adès, J. Cermak, C. Del Canizo, et al. 2013. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood 122:2943–2964.
8. Hoffbrand, A. V., A. Taher, and M. D. Cappellini. 2012. How I treat transfusional iron overload. Blood 120:3657–3669.
9. Temraz, S., V. Santini, K. Musallam, and A. Taher. 2014. Iron overload and chelation therapy in myelodysplastic syndromes. Crit. Rev. Oncol. Hematol. 91:64–73.
10. Malcovati, L., M. Karimi, E. Papaemmanuil, I. Ambaglio, M. Jadersten, M. Jansson, et al. 2015. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood 126:223–241. pii: blood-2015-03-633537.
11. Cermak, J., A. Jonasova, J. Vondrakova, L. Walterova, I. Hochova, M. Siskova, et al. 2011. Efficacy and safety of administration of oral iron chelator deferiprone in patients with early myelodysplastic syndrome. Hemoglobin 35:217–227.

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.