International Journal of Infectious Diseases 122 (2022) 755–757

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

A case of immune complex type hemolytic anemia induced by initial micafungin administration

Hiroto Ishii [1,*], Tomohiko Sato [2], Miyuki Ishibashi [2], Hiroki Yokoyama [1], Takeshi Saito [1], Tetsunori Tasaki [2], Shingo Yano [1]

[1] Division of Clinical Oncology and Hematology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan
[2] Division of Transfusion Medicine and Cell Therapy, The Jikei University Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 14 May 2022
Revised 24 June 2022
Accepted 7 July 2022

Keywords:
Micafungin
Drug-induced immune hemolytic anemia

ABSTRACT

We report the first case of immune complex type hemolytic anemia by initial micafungin administration that was given as prophylaxis to a 42-year-old Japanese man receiving chemotherapy for primary amyloidosis. The few cases found in the literature were associated with secondary administration causing immune hemolytic attacks. Despite its rarity, the present case calls for increased awareness of micafungin-induced hemolytic anemia upon initial administration.

Introduction

Drug-induced hemolytic anemia occurs via immune destruction of red blood cells (RBCs) or destruction due to oxidant injury. Immune-mediated drug-induced hemolysis is mediated by drug-dependent or drug-independent antibodies. The mechanism of drug-dependent reactions can be subdivided into penicillin type, immune complex type, and passive absorption. Immune complex type drug-induced hemolysis is known to be triggered by multiple administrations of the causative drug, in which the complex binds to the RBCs and causes complement activation (Garratty 2010; Garbe *et al.*, 2011). Micafungin, a kind of echinocandin antifungal agent, has come to occupy an increasingly important position in the treatment and prophylaxis of diverse fungal infections. It can also combat azole-resistant strains (Pappas *et al.*, 2016). Its specific fungicidal activity relies on the inhibition of β-1,3-glucan synthase, resulting in growth inhibition of hyphal tips (Hatano *et al.*, 2002). Other than common adverse events, such as rash, flushing, digestive symptoms, and hepatic dysfunction, micafungin rarely causes acute hemolysis. A few previous case reports showed that a resumption of micafungin could trigger acute hemolytic attack via drug-anti-drug immune complex formation (Nanri *et al.*, 2009; Yoshizawa *et al.*, 2010). Here we describe a rarely encountered case of immune complex type hemolytic anemia just after initial micafungin administration.

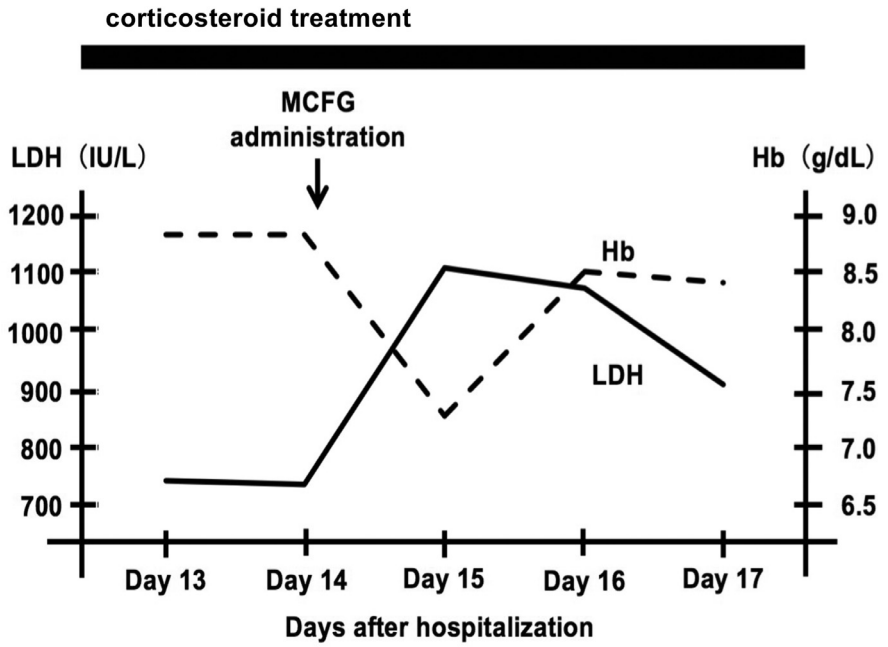
Case presentation

A 42-year-old Japanese man with primary amyloidosis, hypertension, and hypothyroidism was admitted with acute abdominal pain to the intensive care unit (ICU) of our hospital. One year before this admission, the patient had received subcutaneous bortezomib and oral dexamethasone as the first course of treatment for primary amyloidosis with involvement of the liver, kidneys, and autonomic nervous system. Since a contrast-enhanced computed tomography (CT) examination for the present abdominal pain revealed hepatic hemorrhage, the patient underwent catheter embolization of the right hepatic artery and inferior phrenic artery on the admission day (day 0). The patient recovered from related hemorrhagic shock with fluid replacement and RBC_s and plasma transfusions; however, hepatic hemorrhage persisted even after the intervention, forcing him to have absolute bed rest for two more weeks. On day 3 in the ICU, administration of prednisolone (10 mg/day) and itraconazole (200 mg/day) via nasogastric tube was initiated for replacement of oral dexamethasone and prophylaxis of fungal infection, respectively. On day 5, the tube was removed and total parenteral nutrition was started mainly due to transfer from the ICU to a general ward. At the same time, the administration of itraconazole was stopped due to the worsening of hepatic dysfunction. Hepatic hemorrhage and liver dysfunction showed gradual improvement on day 14. During treatment of hepatic hemorrhage,

* Correspondence to: Hiroto Ishii, Division of Clinical Oncology and Hematology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.
E-mail address: h-ishii@jikei.ac.jp (H. Ishii).

https://doi.org/10.1016/j.ijid.2022.07.023

A



B

Direct AGT	Patient's RBCs	
	Pre-MCFG	Post-MCFG
Polyspecific AHG	0	1+
Anti-IgG	0	0
Anti-C3bC3d	0	1+

Immune complex test	
Ficin-treated RBCs	Post-MCFG plasma
+MCFG	1+
+CPFG	0
+MCFG+C	1+
+CPFG+C	0
+PBS	0

Figure 1. (A.) Transitive graph of laboratory data during hemolysis in this case. Hb, hemoglobin; LDH, lactic dehydrogenase; MCFG, micafungin. (B.) Results of direct anti-globulin test (AGT) and immune complex test for this case. AHG, Anti-Human Globulin; CPFG, caspofungin; C, Complement; PBS, Phosphate Buffered Saline; RBC: red blood cell.

transfusions of 1960 mL and 480 mL of allogeneic ABO- RhD-compatible RBC_s (from day 0 to day 4) and plasma (day 3) were required. The patient's hemoglobin (Hb) level was 8.8 g/dL on day 14, with no more requirement for blood transfusion (Figure 1A). Due to persisting oral intake difficulty of the patient, a continuous infusion of prednisolone (10 mg/day) and a drip infusion of micafungin (150 mg/day) were initiated as a replacement on day 15. Dyspnea, flushing, and back pain developed 3 minutes after its administration. With the oxygen saturation of 79% on ambient air, supplemental oxygen therapy of 8 L/min from a non-rebreathing mask was started. Micafungin was discontinued immediately as it was suspected of being a causative agent. Furthermore, 90 minutes later, shivering developed with body temperature elevation up to 40.4°C, and soon afterward dark urine was noted. The dipstick test of the urine was strongly positive for blood and no erythrocytes were detected in the urine sediment. Hb level rapidly decreased to 7.3 g/dL, and lactate dehydrogenase (LDH) level was 1104 U/L (normal range, 124 to 222), indirect bilirubin was 2.2 mg/dL(normal range, below 1.2), and haptoglobin was < 10 mg/dL (normal range, 25-176), confirming acute intravascular hemolysis (Figure 1A). Creatine kinase level was 35 U/L (normal range, 59-248), suggesting that rhabdomyolysis was an unlikely cause of dark urine. Additional abdominal CT scan revealed no recurrence of hepatic or splenic hemorrhage. Blood cultures were negative. With oxygen supplementation and drip infusion of 50 mg hydrocortisone, the related symptoms, such as fever, dyspnea, flushing, and back pain, almost disappeared 8 hours after the onset and micafungin cessation. LDH and indirect bilirubin levels normalized on day 21 and microscopic hematuria completely resolved on day 28.

Due to suspicion of micafungin-induced hemolysis (Hill *et al.*, 2017; Zantek *et al.*, 2012), a direct anti-globulin test was performed. The patient's post-micafungin RBCs showed agglutination, not with anti-IgG but with poly-specific anti-globulin and anti-C3b/C3d anti-globulin, while pre-micafungin RBCs had no agglutination with these agents. The immune complex test (Garratty, 2009), showed agglutination of ficin-treated type O RBCs in a mixture of post-micafungin serum and micafungin (with or without complement), but no agglutination was noted in a mixture of post-micafungin serum and caspofungin, another echinocandin agent (Figure 1B). These data indicate that antibody which can bind to micafungin was produced after the initial micafungin administration, leading to immune complex type hemolytic anemia in this case, and not caused by drug-independent antibodies.

Discussion

This is, to the best of our knowledge, the first report of a case of immune complex type hemolytic anemia following initial micafungin administration, which is a striking contrast to previous reports (Nanri *et al.*, 2009; Yoshizawa *et al.*, 2010). Typically, the development of drug-induced hemolytic anemia of immune complex type requires sensitization and re-administration of the causative drug. This type can cause fatal intravascular hemolysis and show strong positivity in the related immune complex test (Garratty, 2012), which requires prompt cessation of the suspected drug. Considering the short interval between the hepatic hemorrhage and the micafungin-induced hemolytic anemia, delayed cessation of the drug might have led to a fatal outcome, in this case, indicating the importance of careful monitoring of the patient at first-time administration and prompt cessation of micafungin. In addition, it was speculated that continuous corticosteroid treatment for primary amyloidosis might ameliorate the hemolytic attack and weaken the related *in vitro* agglutination (Figure 1B). This case had no prior history of micafungin administration. Despite the structural similarity between micafungin and caspofungin (Mroczyńska and Brillowska-Dąbrowska, 2020), the reactivity of the patient's serum was specific to micafungin, supporting our final diagnosis. However, we could not rule out the possibility that some other previously administered agents with structural similarity to micafungin triggered antibody formation.

In conclusion, despite the rarity, the present case should remind clinicians of micafungin-induced hemolytic anemia even upon initial administration.

Ethical approval

Informed consent was obtained from the patient for publication of this case report.

Authors' contribution

H.I wrote this manuscript. H.I, T.Sato, and M.I analyzed and interpreted the patient data on hemolysis. T.Sato, H.Y, T.Saito, T.T and S.Y. revised this manuscript. All authors read and approved the final manuscript.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors have no competing interests to declare.

References

Garbe E, Andersohn F, Bronder E, Klimpel A, Thomae M, Schrezenmeier H, Hildebrandt M, Späth-Schwalbe E, Grüneisen A, Mayer B, Salama A, Kurtal H. Drug-induced immune haemolytic anaemia in the Berlin Case-Control Surveillance Study. Br J Haematol 2011;154:644–53.

Garratty G. Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program 2009;1:73–9.

Garratty G. Immune hemolytic anemia associated with drug therapy. Blood Rev 2010;24:143–50.

Garratty G. Immune hemolytic anemia caused by drugs. Expert Opin Drug Saf 2012;11:635–42.

Hatano K, Morishita Y, Nakai T, Ikeda F. Antifungal mechanism of FK463 against Candida albicans and Aspergillus fumigatus. J Antibiot (Tokyo) 2002;55:219–22.

Hill QA, Stamps R, Massey E, Grainger JD, Provan D, Hill ABritish Society for Haematology Guidelines. Guidelines on the management of drug-induced immune and secondary autoimmune, hemolytic anemia. Br J Haematol 2017;177:208–20.

Mroczyńska M, Brillowska-Dąbrowska A. Review on current status of echinocandins use. Antibiotics (Basel) 2020;9:227.

Nanri T, Iwanaga E, Fujie S, Yamada Y, Horikawa K, Mitsuya H, Asou N. Micafungin-induced immune hemolysis attacks. Int J Hematol 2009;89:139–41.

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–50.

Yoshizawa S, Gotoh M, Kitahara T, Kiguchi T, Akahane D, Sakuta J, Sunaga K, Ohyashiki K. Micafungin-induced hemolysis attack due to drug-dependent antibody persisting for more than 6 weeks. Leuk Res 2010;34:e60–1.

Zantek ND, Koepsell SA, Tharp DR, Cohn CS. The direct antiglobulin test: A critical step in the evaluation of hemolysis. Am J Hematol 2012;87:707–9.