EJCRIM
European Journal
of Case Reports
in Internal Medicine

THE OUTCOME OF APLASTIC ANAEMIA ASSOCIATED WITH TERBINAFINE THERAPY

Farhan Khalid[1], Sai Rakshith Gaddameedi[1], Ahmad Al-Alwan[1], Husam Bader[1], Doantrang Du[1], Trishala Meghal[2]

[1] Department of Internal Medicine, Monmouth Medical Center, New Jersey, USA
[2] Department of Hematology/Oncology, Monmouth Medical Center, New Jersey, USA

Corresponding author: Sai Rakshith Gaddameedi **e-mail:** Dr.sai.r.gaddameedi22@gmail.com

Received: 23/11/2023 **Accepted:** 05/12/2023 **Published:** 20/12/2023

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: A written informed consent was obtained from the patient for this case report.

How to cite this article: Khalid F, Gaddameedi SR, Al-Alwan A, Bader H, Du D, Meghal T. The outcome of aplastic anaemia associated with terbinafine therapy. *EJCRIM* 2023;**10**:doi:10.12890/2023_004142.

ABSTRACT

Onychomycosis (OM), a widespread fungus that affects the toenails and/or fingernails, causes a large amount of morbidity and is very frequent in the general population. The best treatment is systemic antifungals. Terbinafine is a potent antifungal drug that works by targeting the keratin and lipids found in fungi. In the United States, the prevalence of this nail ailment ranges from 2% to 14%; it is 5.5% globally. Here, we describe a case of aplastic anaemia linked to oral terbinafine use. Clinicians should be aware of this rare adverse effect and early discontinuation of the treatment is required to prevent significant morbidity and mortality.

KEYWORDS

Aplastic anemia, terbinafine, fungi, thrombocytopenia, onychomycosis, pancytopenia

LEARNING POINTS

- Aplastic anaemia is a rare side effect of terbinafine.
- Patients should be advised about this, and serial laboratory testing can be helpful for those who are on a long-term course of terbinafine.
- Early diagnosis and start of treatment can lead to a favourable outcome.

INTRODUCTION

Onychomycosis (OM) is a skin fungal infection of the nails caused by dermatophytes, non-dermatophytic moulds or yeast, and is most caused by *Trichophyton rubrum*. The prevalence of this nail condition ranges from 2% to 14% in the United States and is 5.5% worldwide with age, trauma history of diabetes mellitus, obesity and immunosuppression remaining the significant risk factors[1]. Nail discoloration, separation, brittleness, or thickening are common complaints from patients with OM, which frequently worsens with time. Systemic antifungals are the gold standard treatment[2]. Terbinafine is a potent antifungal medication with a mechanism of action towards fungal lipids and keratin. It has been determined that terbinafine is safe, and any negative effects are often minor and short-lived. It is largely well tolerated but due to its affinity to lipids, in rare cases the use of terbinafine can affect bone marrow and cause neutropenia or pancytopenia, or aplastic anaemia[3].

EFIM European Federation of Internal Medicine

Publisher smc media srl

Here we report a case of aplastic anaemia associated with the use of oral terbinafine.

CASE DESCRIPTION

Our patient was a 42-year-old female with a history of hypothyroidism, iron deficiency anaemia and OM, who presented with generalised bruising of two days' duration. The bruising was noted over the right gluteal region, the calves, and the forearms. No history of trauma was reported; the patient advised that she had been started on terbinafine for recurrent nail infection 2 months prior to the presentation. Her complete blood count at that time showed a white blood count of 6.2 × 10^9/l, a platelet count of 380 × 10^9/l, haemoglobin level of 9.4 g/dl and a ferritin level of 3 µg/l. The patient reported similar self-limited bruising over the anterior chest last year while she was taking terbinafine. A physical examination revealed scattered non-blanching petechiae over the anterior chest and ecchymosis on the left calf, right gluteus and right lower abdomen without lymphadenopathy or organomegaly. Laboratory testing revealed pancytopenia with haemoglobin of 9.2 g/dl, platelet count of 6 × 10^9/l, white blood cell count of 2.1 × 10^9/l and an absolute neutrophil count of 0.4 × 10^3/l. A peripheral smear was consistent with pancytopenia. The reticulocyte count was 0.009 µg/dl; lactate dehydrogenase, fibrinogen, D-dimer, liver function, kidney function and thyroid function tests and vitamin levels were normal. A pan-computed tomography and ultrasound sonography doppler scan of the lower extremities were unremarkable. The patient tested negative for HIV, viral hepatitis, Epstein-Barr virus and parvovirus. Flow cytometry revealed no immunophenotypic evidence of B-cell or T-cell non-Hodgkin lymphoma, or acute leukaemia. Bone marrow biopsy reported only lymphocytes and plasma cells consistent with aplastic anaemia. Terbinafine was withheld; blood cultures and urine cultures remained negative throughout hospitalisation. She started menstruating on day 7 and haemoglobin dropped to 6.6 g/dl with a platelets count of 2 × 10^9/l. She was transferred to ICU for closer monitoring and possible need of massive transfusion initiation and received total of 16 units of platelets and 6 units of packed red blood cells during her hospital stay.

Bone marrow biopsy revealed only lymphocytes and plasma cells, with no evidence of trilineage haematopoiesis *(Fig. 1)*. Staining was negative for CD 34 and CD 117, confirming absence of haematopoietic stem cells *(Fig. 2)*.

Due to persistent pancytopenia and profound neutropenia with an absolute neutrophil count of 0, the decision to administer an immunosuppressive triple therapy (hATG+CsA and Eltrombopag) was made. Her counts improved after therapy on outpatient follow-up.

DISCUSSION

OM is the most prevalent fungal nail infection in the world and causes thickness and discoloration of the nail plate. Diagnosis is largely clinical, but histology and polymerase chain reaction-based tests are more precise diagnostic methods. Microscopy and fungal cultures remain the gold standard approaches. Oral antifungals, topical medications and medical devices are only a few of the potential therapy choices. The most widely used oral antifungals are terbinafine, itraconazole and fluconazole. Novel agents such as fosravuconazole are being tested. Although tools such as lasers have demonstrated promise in enhancing the aesthetics of the nail, their efficacy in treating OM has not yet been satisfactorily established. OM has a high rate of recurrence; once infected, patients should seek medical attention early. OM is treated using systemic drugs that are taken orally since they are readily available, affordable and effective. Due to their high rates of success in treating OM, terbinafine and itraconazole are the most widely prescribed oral antifungals in Europe, the USA, Canada, Japan, and Australia. For all types of OM, oral antifungal medications are recommended, particularly when more than one nail

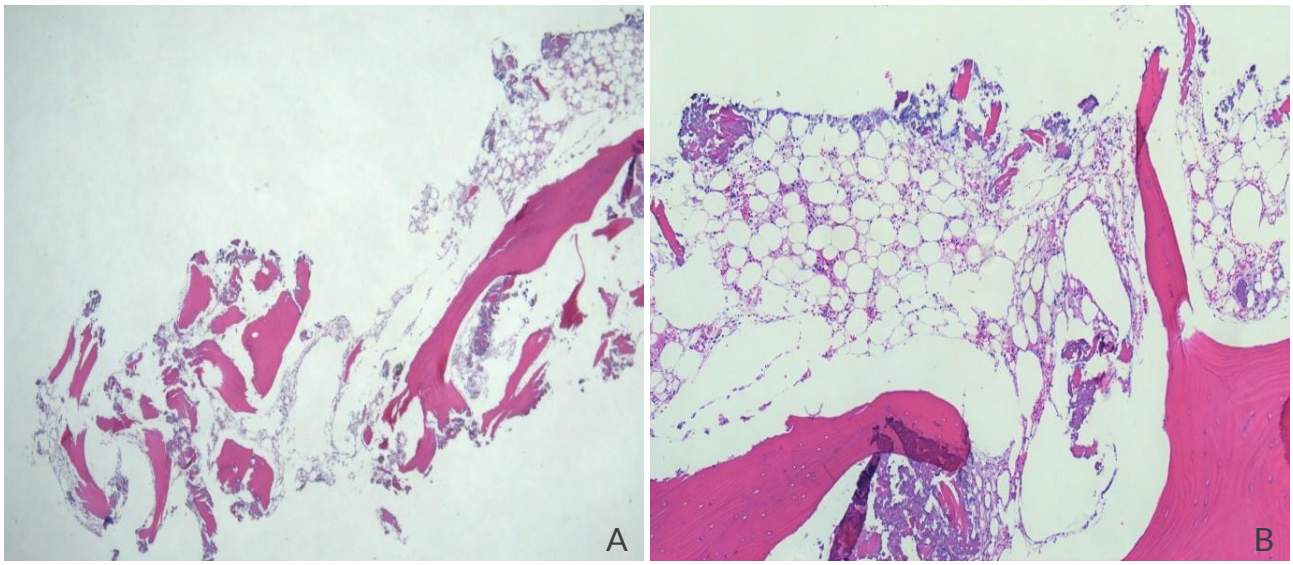

Figure 1. A) Hypocellular bone marrow with lacunar spaces extensively replaced by fatty cells. B) The marrow is devoid of trilineage haematopoiesis. Only lymphocytes and plasma cells are present.

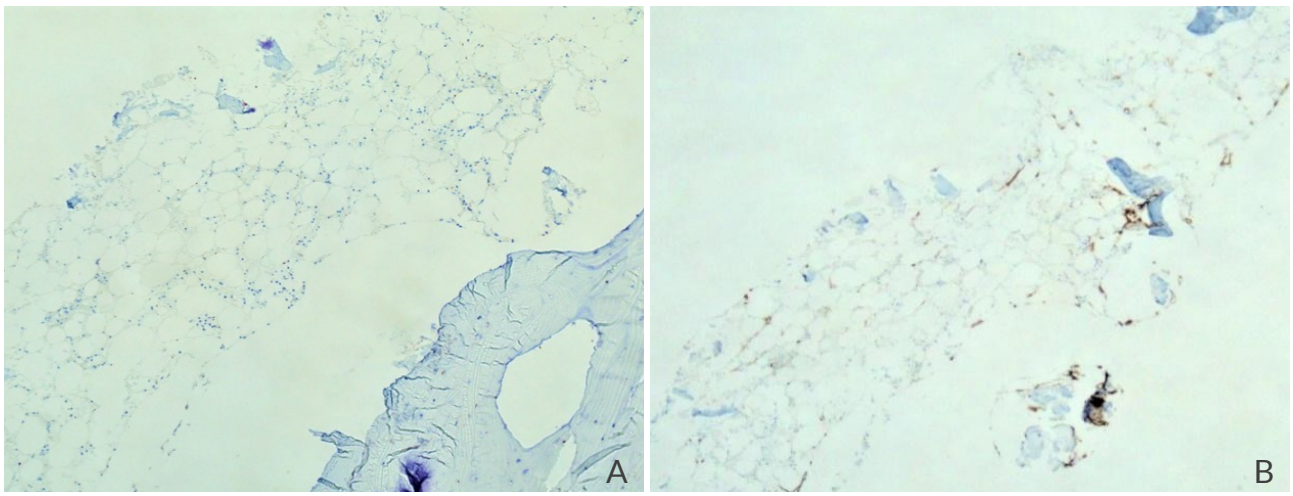

Figure 2. Immunohistochemical stains for CD34 (A) and CD117 (B) show no myeloblasts.

is infected, the nail matrix is involved or dermatophytoma is present. In comparison to topical antifungal medication, oral antifungal therapy has greater cure rates and shorter treatment duration, therefore it is regarded as the gold standard for treating OM in both children and adults[4].

Terbinafine, an allylamine, prevents the production of functional fungal cell membranes by blocking the activity of the enzyme squalene epoxidase *(Fig. 3)*. It has some efficacy against nondermatophytic moulds and is successful in eliminating dermatophytes. For fingernail and toenail infections, the recommended treatment schedule is 250 mg per day for 6 or 12 weeks. Within one week of beginning treatment, it can be found in the distal nail. Headaches, rashes, nausea, vomiting, epigastric discomfort, diarrhoea, drug-to-drug interactions and in rare cases, depression, neutropenia, hepatic dysfunction and Stevens-Johnson syndrome are among the side effects. Agranulocytosis or severe neutropenia, leukopenia, lymphopenia, pancytopenia, thrombocytopenia and anaemia are the haematologic abnormalities associated with terbinafine medication in immunocompetent patients[3]. The blood counts reportedly recovered quickly once the medication was stopped[5].

The mechanism of the immune-mediated damage is proposed to involve several lipophilic medicines' energy-dependent transmembrane efflux pumps such as P-glycoprotein (P-gp), the MDR-1 gene product and the multidrug resistance-associated protein. The under-expression of P-gp in cells allows medicines to accumulate in the cytoplasm and intensify their harmful effects[6].

Terbinafine therapy dramatically enhances the release of IL-8 and the tumour necrosis factor, which further contributes to the immune-mediated damage that can be caused by the drug[7]. Lupus-like symptoms linked to the usage of terbinafine support an immune-mediated process as the underlying mechanism of injury. However, the cause of the aplastic anaemia mechanism's most common trigger is still unknown. According to a review of terbinafine-related haematologic toxicities, terbinafine exposure for over a month starts to cause haematological toxicity; the degree of cytopenia can be severe, and patients typically present with infectious problems that necessitate hospitalisation[8]. In patients receiving the typical 3-month course of terbinafine, liver chemistry tests and complete blood count should be evaluated every 4 to 6 weeks. Patients starting treatment should be informed of the signs and symptoms of terbinafine side effects, as well as the necessity to follow up. Our patient scored 7 points on the adverse drug reaction probability (Naranjo score) scale *(Table 1)* which indicates probable association of terbinafine with aplastic anaemia[9].

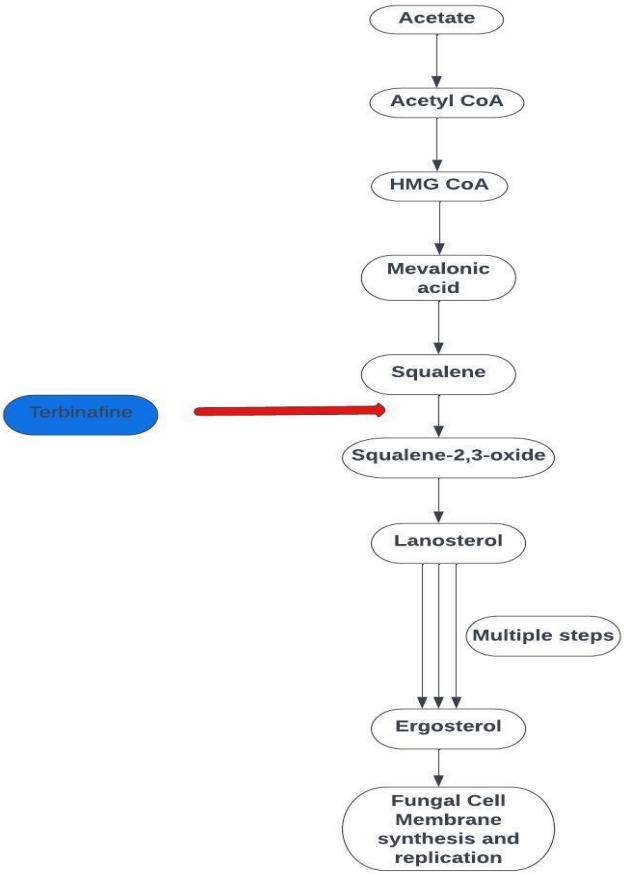

Figure 3. Flow chart: Terbinafine - Mechanism of action.

Naranjo Adverse Drug Reaction Probability Scale				
Question	**Yes**	**No**	**Do Not Know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	−1	0	0
5. Are there alternative causes (other than the drug) that could have caused the reaction on their own?	−1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	+1
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE				**7**

Table 1. The Naranjo score[9] of terbinafine association with aplastic anaemia.

REFERENCES

1. Lipner SR, Scher RK. Onychomycosis: clinical overview and diagnosis. *J Am Acad Dermatol* 2019;**80**:835–851.
2. Bodman MA, Krishnamurthy K. Onychomycosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
3. Conjeevaram G, Vongthavaravat V, Sumner R, Koff RS. Terbinafine-induced hepatitis and pancytopenia. *Dig Dis Sci* 2001;**46**:1714–1716.
4. Gupta AK, Stec N, Summerbell RC, Shear NH, Piguet V, Tosti A, et al. Onychomycosis: a review. *J Eur Acad Dermatol Venereol* 2020;**34**:1972–1990.
5. Kovacs MJ, Alshammari S, Guenther L, Bourcier M. Neutropenia and pancytopenia associated with oral terbinafine. *J Am Acad Dermatol* 1994;**31**:806.
6. Gupta AK, Soori GS, Del Rosso JQ, Bartos PB, Shear NH. Severe neutropenia associated with oral terbinafine therapy. *J Am Acad Dermatol* 1998;**38**:765–767.
7. Scheinberg P. Aplastic anemia: therapeutic updates in immunosuppression and transplantation. *Hematology Am Soc Hematol Educ Program* 2012;**2012**:292–300.
8. Kantarcıoğlu B, Türköz HK, Yılmaz G, Pepedil Tanrıkulu F, Kaygusuz Atagündüz I, Adıgüzel C, et al. Aplastic anemia associated with oral terbinafine: a case report and review of the literature. *Turk J Haematol* 2014;**31**:411–416.
9. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–245.