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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 5

Melanosis of hand and foot caused by ibrutinib: A case report

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Received: Jul 04, 2024

Accepted: Jul 23, 2024

Published: Jul 30, 2024

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/1532

Abstract

Ibrutinib is a potent covalent inhibitor of Bruton's Tyrosine Kinase (BTK), a downstream kinase of B cell receptor vital for B cell survival and proliferation. Ibrutininb is indicated to treat many types of B- lymphoproliferative disorders, including Mantle Cell Lymphoma (MCL). Ibrutininb is considered a well-tolerated drug, with a small side effect profile compared to chemotherapy. Side effects include diarrhea, bleeding tendency, hypertension, atrial fibrillation and rarely, secondary malignancies reported at generally low frequency. Here we report a case with a relapse of MCL who developed melanosis of the hands and feet upon treatment with Ibrutinib, with complete resolution of the phenomenon upon discontinuation of drug.

Keywords: Mantel cell lymphoma (MCL); Ibrutinib; Melanosis.

Introduction

Mantle Cell Lymphoma (MCL) is an aggressive form of mature B cell non-Hodgkin lymphoma characterized by involvement of lymph nodes, spleen, blood and bone marrow with a short remission duration to standard therapies with overall survival of ~ 4-5 yrs [1]. MCL is more common in men and median age of diagnosis ranges 60 to 70 years old. An excisional or incisional biopsy of involved lymph node or extra nodal site or bone marrow trephine biopsy is needed to diagnose B cell lymphoma. MCL cells often have CD5, CD20, BCL2 and high levels of cyclin D1. Cases are typically diagnosed with diffuse cyclin D1 positivity by immunohistochemistry or Fluorescence In-Situ Hybridization (FISH) for t(11,14), rare cases negative for cyclin D1 for t(11,14) are positive for SOX11 by immunohistochemistry [2].

Treatment broadly consists of 2 components-cytarabine containing induction chemotherapy followed by ASCT (Autologous Stem Cell Transplantation), several regimens are available depending upon patient belonging to fit, unfit, maintenance or relapsed category which target either Bruton's Tyrosine Kinase (BTK), antiCD20 or BCL2 [3].

Ibrutinib is a potent covalent inhibitor of BTK a kinase downstream of B cell receptor that is critical for B cell survival and proliferation. In clinical studies it has found to be well tolerated and has demonstrated profound antitumor activity in variety of hematological malignancies like mantle cell lymphoma, CLL, Waldenstrom's macroglobulinemia, diffuse large B cell lymphoma [4]. Ibrutinib is widely being used for previously unmet needs, i.e., for patients with relapsed or refractory disease, high-risk cytogenetic or molecular abnormalities, or with comorbidities [8].

Immunotherapeutic drugs often have toxicities, which are different from many known or unknown side effects. Most common side effects associated with ibrutinib are diarrhea, upper respiratory tract infection, bleeding, fatigue and cardiac side effects. These events are generally mild (grade 1-11). However Atrial fibrillation and bleeding are important and may be grade 3 [5]. Other common side effects are arthralgia, nausea, vomiting, dehydration, dizziness, headache. Rare side effects include giant hives, hardening of liver, kidney failure, liver failure, panniculitis, Steven Johnson syndrome, basal cell carcinoma, squa-

mous cell carcinoma, melanosis coli have been reported. Here we report a side effect of Ibrutinib which has not been reported till now- Melanosis of hands and feet.

Case presentation

74-year-old female with past medical history of hyperlipidemia, anxiety, depression presented to the outpatient clinic with cervical and inguinal adenopathy in 2012. Biopsy of the right neck mass showed evidence of mantle cell lymphoma, with expression of CD20, CD19, CD5, FMC 7 and cyclin D1. Staging studies showed multiple abdominal lymphadenopathy and 70% involvement of the bone marrow making her stage IV A. She was treated with 2 cycles of RMCHOP leading to good response. She was transitioned to EAR conditioning regimen for autologous bone marrow transplant, but she developed neutropenic fever, mucositis, deconditioning and debilitating depression/anxiety and was hospitalized in 2012. Later restaging studies showed complete response and transplant was cancelled.

2 years later in 2014, patient presented with progressive lymphadenopathy, fine needle aspiration biopsy of supraclavicular node confirmed relapse of mantle cell lymphoma. She was treated with 6 cycles of Bendamustine and Rituximab, achieved complete response by January 2015. She was on maintenance therapy with rituximab until February 2016.

In February 2016, patient presented with multiple subcutaneous nodules, biopsy proved recurrent mantle cell lymphoma. Patient was enrolled in Ohio State University (OSU) protocol 13022 and she was started on Ibrutinib and Revlimid. She had good response but due to recurrent sinus infection and aspergillus lung infections, she was off treatment for 4 months.

In 2017, patient presented with right calf mass, which was biopsy proven recurrent disease. She was started on ibrutinib at this time. Patient tolerated it well without any diarrhea, recurrent sinus infections and cutaneous manifestations.

In 2018, patient was noted to have abnormal pigmentation changes in hand and feet (Figures 1 and 2). She mentioned she had the same symptoms when she was on Ibrutinib previously. At this time, ibrutinib manufacturer was contacted to discuss about occurrence of melanosis as a side effect of ibrutinib but manufacturer wasn't aware of any such. The patient was continued on ibrutinib as she was tolerating it well otherwise.

In may 2019, her disease progressed and melanosis worsened (Figure 3). Ibrutinib was discontinued and was started on rituximab and revlimid as per Ohio State University recommendations.

Melanosis resolved after stopping ibrutinib (noticed in July 2019) (Figure 4).

Discussion

Ibrutinib, a Bruton Tyrosine Kinase inhibitor, is used for management of CLL, relapse mantle cell lymphoma and Waldenström macroglobulinemia. Many side effects were reported including severe fungal infections, cardiac side effects including atrial fibrillation, ventricular arrythmia, sudden cardiac death, autoimmune side effects including AIHA, bleeding, rare nail abnormalities [6,8]. Cutaneous manifestations also have been reported in 2 to 27% of patients receiving Ibrutinib described

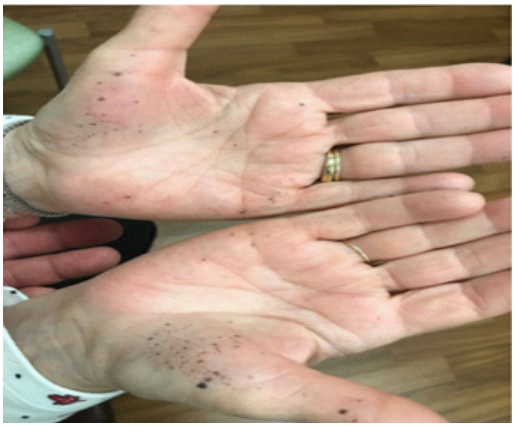

Figure 1: Clinical image.

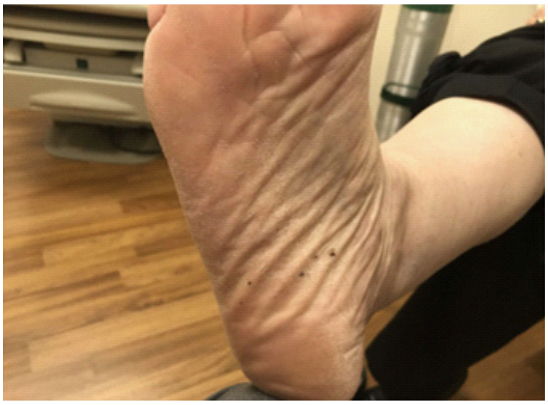

Figure 2: Clinical image.

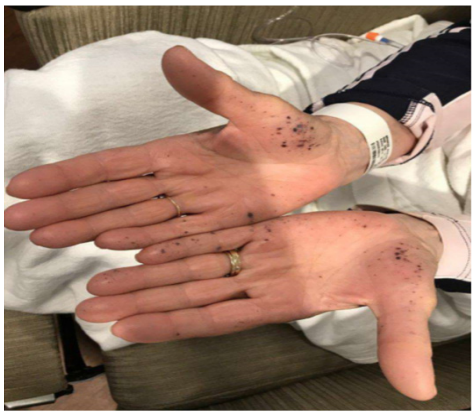

Figure 3: Clinical image.

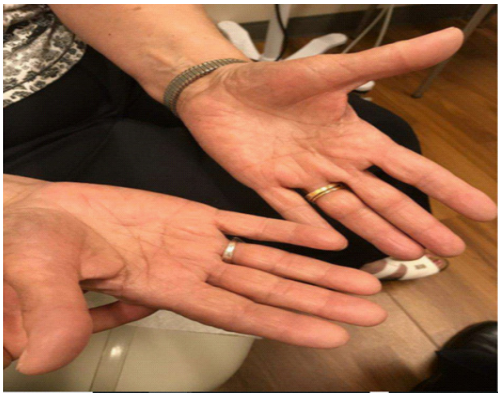

Figure 4: Clinical image.

as rash, petechiae, bruising [7]. Other common side effects like Nausea, vomiting, constipation, diarrhea, dizziness, headache Ibrutinib have also been reported as minor side effects of the drug [9].

Further a single center study was done at Stanford cancer center where data were collected through retrospective chart review which identified two presentations of Ibrutinib associated rash- a non-palpable petechial eruption and a palpable purpuric rash which were treated with topical therapy and oral antihistamines, adding systemic corticosteroids and temporary interruption of Ibrutinib for severe rash were recommended to handle the side effects [8].

Conclusion

Though Ibritunib associated skin toxicity (maculo papular rash) has been reported in previous studies, but melanosis has not been reported as of our knowledge. Melanosis of the colon has been reported but this was thought to be due to the tumor colonic involvement rather than the drug. Imitanib, another tyrosine kinase inhibitor; another drug from the same family, has been reported to cause oral melanosis [10]. Here we report melanosis of hand and feet which appear after starting Ibrutunib, worsened on continuing and resolved after stopping ibrutinib.

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