Ibrutinib Induced Skin Rash

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15 March 2020
13 October 2020

To the Editor,

Ibrutinib is an oral irreversible inhibitor of Bruton’s tyrosine kinase, a B-cell receptor kinase, has been approved for use in chronic lymphocytic lymphoma (CLL); mantle cell lymphoma and Waldenstrom macroglobulinemia. Cutaneous side effects of ibrutinib have been rarely reported and the most common presentation is skin rash [1]. We report an elderly patient of relapsed CLL who developed severe skin rash within a week from start of ibrutinib, reappeared after introduction of lower doses and required further discontinuation of drug.

A 66-year-old obese male, known case of CLL (RAI stage –II) presented with rapid doubling of absolute lymphocyte count and fatigue after a observation of 3 years. He had 13q deletion on fluorescent-in-situ hybridisation. He also had comorbidities of hypothyroidism and idiopathic dilated cardiomyopathy with baseline left ventricular ejection fraction of 35%. He was started on Ibrutinib 420mg once daily. Concurrently he was also receiving levothyroxine, aspirin, atorvastatin and furosemide tablets since last 10 years. On fourth day of start of ibrutinib, he developed severely itchy grade 3 maculopapular rash involving nape of the neck, trunk, axilla, limbs and groin area without any fever or symptoms of systemic allergy (Fig1a,b). We attributed the rash as a side effect of ibrutinib because there were no confounding factors explaining the cutaneous findings. Ibrutinib was stopped and he was referred to a dermatologist. Skin rash responded to oral steroids and antihistamines with complete resolution by day 14. A punch biopsy specimen was taken and histopathological examination revealed features suggestive of leucocytoclastic vasculitis (perivascular inflammatory exudates with extravasation of RBCs) with elevated eosinophils consistent with drug eruption (Fig1c,d). Ibrutinib re-challenge was attempted with a dose of 140mg once daily however, he developed similar grade III rash after a 3 days. Rash disappeared after 15 days of stopping ibrutinib and administration of systemic steroids necessitating permanent discontinuation of culprit drug.
the last outpatient follow up, patient was doing well on Infusional chemo immunotherapy and disease is in remission after 3 cycles

Although ibrutinib is a highly selective BTK inhibitor, it exerts off target effects on other kinases like epithelial growth factor receptor (EGFR) leading to inhibition of cell cycle progression and increased apoptosis. The inhibition of EGFR appears to be the most likely mechanism of ibrutinib induced skin rash. Another proposed mechanism of ibrutinib induced drug eruption is via inhibition of ckit and PDGFR (platelet derived growth factor receptor) [2,3]. So far, few case reports, mostly in western population, have reported three types of ibrutinib induced skin rash- a leucocytoclastic vasculitis like pruritic violaceous palpable purpura, painless non pruritic edematous papules with centripetal spread and a third variety of asymptomatic non palpable petechial rash [1,3]. Almost all of these were grade 1 or 2 in severity and were treated symptomatically with topical steroids and antihistamines without discontinuation of ibrutinib. To our knowledge, this is the first report from India where ibrutinib caused severe skin toxicity that required drug discontinuation and the mechanism is most probably due to hypersensitivity as there were abundant eosinophils in histopathology specimen. With the availability of generic form of ibrutinib in India and its increasing demand in CLL, MCL and newer indications like chronic graft versus host disease, it is important to correctly identify and manage ibrutinib induced skin toxicity.

References