A case of hepatotoxicity associated with vismodegib

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INTRODUCTION

Most basal cell carcinomas (BCCs) contain a loss of function mutation in the tumor suppressor gene *PTCH1*, which results in alterations in the hedgehog signaling pathway.[1] The product of the *PTCH1* gene is patched protein, a 12-transmembrane receptor that normally acts to inhibit the signaling activity of smoothened homologue (SMO), a G-protein coupled receptor.[2] When a mutation in *PTCH1* occurs, SMO cannot be inhibited, and the hedgehog pathway remains constitutively active, resulting in an uncontrolled proliferation of basal cells.[2] Local mutations in the *PTCH1* gene can lead to a single BCC, whereas genetically inherited mutations in *PTCH1*, as seen in basal cell nevus syndrome, often result in the formation of multiple BCCs.[3]

Although most BCCs are readily treated by surgery, advanced or metastatic lesions may no longer be responsive to standard treatments and may necessitate systemic therapy.[1] Vismodegib is a first-in-class drug that was approved in 2012 to treat locally advanced or metastatic BCC.[4] It functions as a small-molecule inhibitor that binds to and inhibits SMO, resulting in the blockade of the hedgehog signaling pathway.[1] The efficacy and pharmacokinetics of vismodegib have been evaluated in multiple clinical studies, which included patients with advanced BCC.[1,2] The most commonly reported adverse events associated with vismodegib are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea.[1,2]

Hepatotoxicity associated with vismodegib is a rare occurrence that has been detected in postmarketing surveillance studies.[4,5] However, safety notifications related to hepatotoxicity have not been issued by the manufacturer or the US Food and Drug Administration (FDA).[5] There have also been limited published case reports of this adverse reaction.[3,6-8] We present a case of hepatotoxicity associated with the use of vismodegib in a patient with previously undiagnosed hepatic steatosis and asymptomatic cholelithiasis.

Abbreviations used:

BCC: basal cell carcinoma
LFT: liver function tests
SMO: smoothened homologue

CASE PRESENTATION

A 54-year-old white man presented with a locally advanced BCC on the forehead (Fig 1). He was given vismodegib, 150 mg/d, with noted improvement in the size of the lesion on day 25 of treatment (Fig 2). At day 25, he was tolerating treatment well with only minor complaints of muscle cramps, hypogeusia, and dysgeusia. Over the following week, however, he had acute onset of generalized pruritus, most severe on his arms, and yellowing of his skin and eyes. Physical examination found significant jaundice, scleral icterus, and numerous excoriations over the bilateral dorsal forearms. He had no fever, chills, weight loss, or abdominal pain and denied a history of liver disease, hepatitis, or alcohol use. The patient also denied concurrent use of any hepatotoxic medications; he was only taking lisinopril, 10 mg/d, and using topical imiquimod for the treatment of

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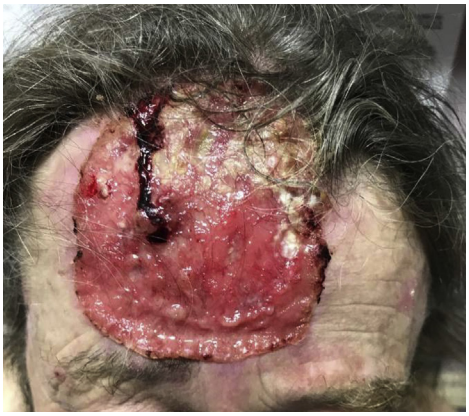

Fig 1. Initial presentation of patient with locally advanced BCC of the forehead.

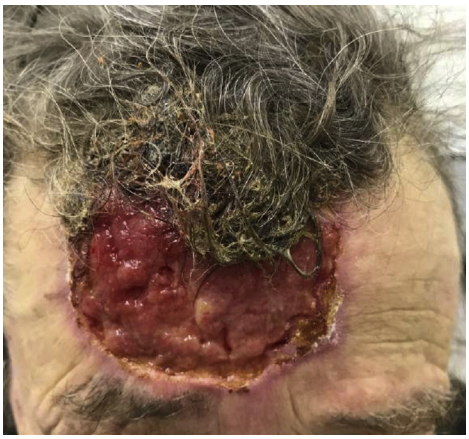

Fig 2. Reduction in size of locally advanced BCC after 25 days of treatment with vismodegib.

squamous cell carcinoma in situ. Liver function tests (LFTs) found elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin (Table I). Vismodegib was discontinued at that time, and the patient was referred to the emergency department for further evaluation. At time of admission 1 day later, he had an elevated gamma glutamyl transpeptidase with worsening transaminitis (Table I). His albumin and prothrombin time/international normalized ratio were within normal limits. Serology for HIV and hepatitis A, B, and C were negative. Ultrasound scan found hepatic steatosis with no evidence of cirrhosis. Cholelithiasis was present without signs of acute cholecystitis or biliary tree dilatation. The patient remained hospitalized for 2 days and was discharged after improvement in symptoms and display of downward trending LFTs (Table I).

Table I. Patient laboratory values

Days after initiating vismodegib therapy	32	33	34	35
Total bilirubin (mg/dL)	6.3	4.7	4.2	2.2
Indirect bilirubin (mg/dL)	1.3	1.3	1.5	1.1
Direct Bilirubin (mg/dL)	5	3.4	2.7	1.1
ALK PHOS (U/l)	304	327	309	304
ALT (U/l)	151	167	147	138
AST (U/l)	83	103	96	87
GGT (U/l)	-	496	-	-

ALT, Alanine aminotransferase; *ALK* PHOS, alkaline phosphatase; *AST*, aspartate aminotransferase; *GGT*, gamma glutamyl transpeptidase.

DISCUSSION

Hepatotoxicity associated with vismodegib is a rare but serious side effect. In a postmarketing surveillance study conducted by Edwards et al,[5] 94 cases associated with at least 1 adverse event of liver dysfunction were reported between 2009 and 2015 in the US Food and Drug Administration Adverse Event Reporting System. Of these cases, 34 had severe hepatotoxicity with 20 cases resulting in hospitalization or death. An explanation for the cause of hepatotoxicity in patients taking vismodegib has yet to be established. Only a few published case reports offer potential explanations.

One case of severe hepatic injury was reported in an 83-year-old woman with a history moderate daily alcohol use.[8] This patient had nausea and vomiting after 1 week of treatment and was hospitalized 3 weeks later. Liver function tests found a cholestatic pattern of hepatotoxicity, and liver biopsy found nonspecific cholestasis with portal fibrosis.[8] Chronic alcohol use was suggested to have been a predisposing risk factor for the hepatic injury.[8] Ash and Jolly[3] reported a case of a 72-year-old man who had hepatotoxicity while also taking nonsteroidal anti-inflammatory drugs (NSAIDs) including naproxen to treat his myalgias caused by vismodegib. Although uncommon, direct hepatic injury from aspirin and naproxen has been reported.[9,10] Naproxen is not known to independently increase aminotransferase enzymes, thus the hepatotoxicity in this case was attributed to the combination of vismodegib and nonsteroidal anti-inflammatory drugs.[3] Finally, Vestita et al[7] reported on a 71-year-old man with a history of asymptomatic cholelithiasis who had jaundice and acute liver injury after 3 months of vismodegib. His laboratory work showed cholestatic injury, and imaging found microlithiasis with acute cholestasis. It was hypothesized that vismodegib caused increased bile density, which led to hepatic injury in the setting of pre-existing cholelithiasis.[7]

Our patient was not taking any drugs associated with liver injury nor did he have a history of alcohol abuse or hepatitis. Imaging showed hepatic steatosis

and the presence of cholelithiasis without signs of acute cholestasis. It is possible that his previously undiagnosed hepatic steatosis and/or cholelithiasis predisposed him to liver toxicity while on vismodegib. Therefore, it may be prudent to check baseline LFTs before initiating vismodegib and to exercise caution when prescribing it to patients with known hepatic impairment. Given the limited number of case reports, the association between vismodegib and hepatotoxicity remains unclear. Further investigation is needed to learn more about this potential relationship.

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