Cholestasis in a Patient of Multiple Myeloma: A Rare Occurrence of Bortezomib Induced Liver Injury

Ankur Jain¹ · Pankaj Malhotra¹ · Vikas Suri¹ · Subhash Varma¹ · Ashim Das² · Suvradeep Mitra²

Received: 8 January 2016 / Accepted: 24 February 2016 / Published online: 1 March 2016
© Indian Society of Haematology & Transfusion Medicine 2016

Drug induced liver injury (DILI) is a common cause of jaundice (2–10 %) in hospitalized settings. Diagnosing DILI clinically is a dogmatic task as DILI can mimic almost any cause of acute or chronic hepatitis. Lack of specific clinical, biochemical or imaging findings and concomitant systemic illness makes DILI a diagnosis of exclusion, recognition of which is extremely important to prevent long term hepatic injury. [1] We report a 54 years-old non-alcoholic man who initially presented to our hematology clinic with complaints of backache of 3 months duration. Investigations revealed anemia (Hb: 8 g/dl), renal failure (Creatinine: 3.2 mg/dl), hypercalcemia (calcium: 12.4 mg/dl), sedimentation rate of 98 mm/h and punched out Lytic lesions in skull, pelvis and vertebrae. Bone marrow aspirate revealed 32 % plasma cells. Serum protein electrophoresis (SPEP) with immune-fixation identified monoclonal (M) band (4.2 g/l, IgG Kappa), thereby confirming a diagnosis of Multiple myeloma ISS-II

($\beta 2$ microglobulin—4 mg/dl). Urine electrophoresis and Bence jones proteins were negative. Liver function tests (LFT) and viral serologies for hepatitis B, hepatitis C and HIV were normal. Hypercalcemia and renal dysfunction were managed with saline hydration and bisphosphonates followed by a combination of oral Cyclophosphamide (300 mg/m²) and dexamethasone (40 mg) administered weekly and bortezomib (1.3 mg/m²) on day 1, 4, 8 and 11 in a 4 weekly schedule (CyBorD). Cotrimoxazole and Acyclovir were used as prophylaxis for *Pneumocystis jiroveci* and herpes zoster respectively. Serum calcium and Creatinine levels normalized following the first cycle. Patient presented currently with jaundice and pruritus 2 days after receiving second dose of bortezomib during second cycle of CyBorD. He denied any fever, abdominal pain and herbal drug intake. Patient was conscious, oriented to time, place and person with blood pressure—120/72 mm hg, pulse rate—72/min. General examination revealed marked icterus without any features of hepatic encephalopathy. Abdomen examination revealed hepatomegaly (4 cm) in the absence of free fluid or splenomegaly. Rest of the systemic examination was unremarkable. Laboratory investigations revealed Hb—8.8 g/dL, white cell counts—570 $\times 10^9$ /l, differential counts—68 % polymorphs, 22 % lymphocytes, 8 % monocytes and 2 % eosinophils, platelets—533 $\times 10^9$ /l, sedimentation rate—45 mm/hour, total bilirubin—15.50 mg/dl, direct fraction—12.97 mg/dl, Aspartate aminotransferase—235 U/L, Alanine aminotransferase—367 U/L, Alkaline phosphatase—2456 U/L, G-Glutamyl transferase—264 U/L, Lactate dehydrogenase—450 U/L. Coagulation profile (Prothrombin time, activated partial thromboplastin time and D-dimers, fibrinogen), Viral serologies for hepatitis A (IgM), Australia antigen (HBsAg), hepatitis C (anti-HCV), hepatitis E (IgM),

✉ Pankaj Malhotra
hematpgi@gmail.com; malhotrapankaj@hotmail.com

Ankur Jain
drankur589@yahoo.in

Vikas Suri
surivikas9479@gmail.com

Subhash Varma
suvarma@gmail.com

Ashim Das
Ashim126@gmail.com

Suvradeep Mitra
sugreebm@gmail.com

¹ Department of Hematology, 4th Floor, Nehru Hospital, PGIMER, Chandigarh, India

² Department of Histopathology, PGIMER, Chandigarh, India

Epstein Barr virus (IgG and IgM), cytomegalovirus (IgM and DNA by PCR), and HIV-1 and 2 (by ELISA) were normal. Autoimmune workup including antinuclear (ANA), double stranded DNA (dsDNA), smooth muscle antigen (SMA), liver kidney microsome (LKM) and anti-mitochondrial (AMA) antibodies was negative. Workup for tropical infections (malarial antigen and serology, IgG for RK-39 antigen and aldehyde for leishmania, IgM for scrub typhus and IgM dengue, blood culture for salmonella, procalcitonin), hemolytic work up (plasma hemoglobin, urine for hemosiderin, G6PD assay and Coomb's test), 2D-echocardiography and Ultrasound abdomen (USG) was normal [except for hepatomegaly (17 cm)]. A normal MRCP abdomen ruled out extrinsic compression as a cause of cholestasis. Patient achieved a very good partial response (VGPR) of myeloma (negative SPEP and urine electrophoresis, but positive immunofixation). Abdominal fat pad biopsy was negative for amyloid. A percutaneous liver biopsy was performed which revealed maintained lobular architecture with inflamed portal tracts. There was a mild to moderate lymphoplasmacytic infiltrate with focal eosinophilic infiltration and intracanalicular and intracytoplasmic cholestasis in the centrizonal region suggestive of drug induced hepatitis (Figs. 1, 2). There was no evidence of plasma cell infiltration or amyloid deposition in the liver. Considering a possibility of DILI, Cyclophosphamide and bortezomib were stopped and patient was started on thalidomide based regimen (Thalidomide 100 mg daily and dexamethasone 40 mg weekly). Conservative management with ursodeoxycholic acid led to normalisation of LFTs gradually over 4 weeks. After normalization of the LFTs, Cyclophosphamide was reintroduced in the treatment (300 mg/m² weekly) along with thalidomide (100 mg daily), dexamethasone (40 mg

Fig. 1 Photomicrograph shows maintained lobular architecture with mild lymphomononuclear portal tract infiltrate (red arrow) and midzonal intrahepatocytic and intracanalicular cholestasis (black arrow) (Hematoxylin and Eosin; $\times 100$) (color figure online)

Fig. 2 Higher magnification highlights bland cholestasis (black arrow) with occasional focus of lobular inflammation (red arrow) (Hematoxylin and Eosin; $\times 400$) (color figure online)

weekly) [CTD regimen], Cotrimoxazole and Acyclovir. Reintroduction of Cyclophosphamide, Cotrimoxazole and acyclovir was well tolerated without any recurrence of hepatitis and therefore, bortezomib was implicated as a culprit agent in severe cholestasis. Patient achieved CR after two cycles of CTD and was planned for autologous stem cell transplantation. Although at autopsy 45 % cases show plasma cell infiltration in the liver, clinical liver involvement in multiple myeloma is unusual [2]. Liver involvement in myeloma can take multiple forms including extramedullary plasmacytoma (space occupying lesion), light chain deposition, amyloidosis or diffuse plasma cell infiltration. Clinical manifestations vary from asymptomatic elevation of ALP with normal or slightly elevated aminotransferase levels to liver failure secondary to massive plasma cell or amyloid infiltration [2, 3]. Treatment of myeloma is plagued by DILI as vinca alkaloids and anthracyclins are hepatotoxic and thalidomide may also be hepatotoxic. Steroids and bortezomib were considered hepato-safe in myeloma till recently when concerns were raised regarding bortezomib induced hepatotoxicity. [2, 4] Thrombocytopenia, peripheral neuropathy and gastrointestinal side effects are the most commonly reported adverse events with bortezomib [5]. Since its first recognition in 2005 by Rosinol et al. [6], few cases of bortezomib induced hepatitis have been described thereafter. Kim et al. [5] reported a 52-years old myeloma patient who developed severe hepatitis 3 days after the second dose of bortezomib characterized by normal bilirubin and an elevated aminotransferase levels (out of proportion to ALP) which settled in 2 weeks of stopping bortezomib. Bortezomib induced liver changes includes pigment deposition in hepatocytes, vacuolization and hepatocellular hypertrophy [5]. Chalasani et al. [7] recently proposed an algorithm

for the diagnosis and management of DILI according to 'R' value ($\text{ALT/ALT ULN} \div \text{ALP/ALP ULN}$, where $R < 2$, $2-5$ and >5 indicates cholestasis, mixed and hepatocellular pattern respectively). Our patient developed a cholestatic pattern of injury (R value—0.46) during second cycle of bortezomib therapy which resolved gradually over 4 weeks of stopping bortezomib. This is in contrast to previously reported hepatocellular pattern seen with bortezomib. Since, reintroduction of Cyclophosphamide, Cotrimoxazole and Acyclovir in the treatment was well tolerated without any recurrence of hepatic derangement, bortezomib was the likely culprit in our case and hence, rechallenge with this novel agent was not attempted. Attainment of CR with thalidomide based regimen strengthens the fact that there is no cross-hepatotoxicity between proteasome inhibitors and immunomodulators (thalidomide). Current case describes a previously unreported cholestatic pattern of injury with bortezomib and highlights the fact that even *delayed* hepatotoxicity may be seen with the use of this novel agent, obligating periodic monitoring of LFT during its use.

Compliance with Ethical Standards

The article complies with the ethical guidelines as per the Helsinki declaration.

Conflict of interest The authors declare no conflicts of interests.

Consent for Publication Consent for publication was obtained from the patient prior to the submission of the article.

References

1. Vuppalanchi R, Liangpunsakul S, Chalasani N (2007) Etiology of new-onset jaundice: how often is it caused by idiosyncratic drug-induced liver injury in the United States? *Am J Gastroenterol* 102:558–562
2. Rahhal FE, Schade RR, Nayak A, Coleman TA (2009) Hepatic failure caused by plasma cell infiltration in multiple Myeloma. *World J Gastroenterol* 15:2038–2040
3. Malhotra P, Bhat P, Mahi S, Chauhan S, Rajwanshi A, Varma S (2005) Evolution of hepatosplenic plasmacytoma in a patient with multiple myeloma receiving chemotherapy. *Am J Hematol* 78:82–83
4. Trojan A, Chasse E, Gay B, Pichert G, Taverna C (2003) Severe hepatic toxicity due to thalidomide in relapsed multiple myeloma. *Ann Oncol* 14:501–502
5. Kim Y, Kim KY, Lee SH, Chung YY, Yahng SA, Lee SE, Park G (2012) A case of drug-induced hepatitis due to bortezomib in multiple myeloma. *Immune Netw* 12:126–128
6. Rosiñol L, Montoto S, Cibeira MT, Bladé J (2005) Bortezomib-induced severe hepatitis in multiple myeloma: a case report. *Arch Intern Med* 165:464–465
7. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ (2014) ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 109:950–966