Abstract. Background: Lenalidomide is an immunomodulatory drug frequently used for treatment of patients with multiple myeloma and myelodysplastic syndromes. This report presents a rare case of lenalidomide-associated hepatotoxicity and reviews the available literature. Case Report: A 67-year-old male with multiple myeloma was hospitalized with nausea, vomiting and jaundice, while treated with a second three-week course of lenalidomide. The patient was found to have acutely elevated bilirubin, alkaline phosphatase, AST and ALT. He also had acute on chronic renal function impairment. Serology for viral hepatitis, abdominal ultrasound, magnetic resonance cholangiopancreatography and hepatobiliary scan revealed no abnormalities. Lenalidomide was stopped, resulting in subsequent (8 days) clinical improvement and normalization of the liver abnormalities. The RUCAM causality assessment score was 8, consistent with probable lenalidomide-associated hepatotoxicity. Literature review revealed four other published cases of lenalidomide-associated hepatotoxicity with clinical presentation varying between cholestatic-, hepatocellular- or mixed-pattern of liver injury. All patients had clinical and laboratory improvement soon after lenalidomide discontinuation. Renal function impairment was present in 3 of the 5 reported cases. The exact mechanism of lenalidomide-associated liver injury remains unclear as only 2 patients had liver biopsies without specific findings. Conclusion: Physicians should be aware of the potential for lenalidomide-associated hepatotoxicity, particularly in patients with underlying renal insufficiency.

Background

Lenalidomide is an immunomodulatory drug that is currently being increasingly used for the treatment of patients with relapsed or refractory multiple myeloma (MM), and low or intermediate risk myelodysplastic syndromes (MDS) (1, 2). The drug is typically given as an oral, 25 mg/day (MM) or 10 mg/day (MDS), on days 1 through 21 in repeated 28-day cycles (combined with dexamethasone for MM). There are limited data on hepatotoxicity related to this medication. We present a rare case of lenalidomide-associated hepatotoxicity and review the available literature.

Case Presentation

A 67-year-old male with known IgG lambda MM and previously normal liver biochemical examination results was hospitalized with a 2-week history of nausea, vomiting, fatigue and jaundice. The patient was receiving a second three week course of lenalidomide (25 mg/day) and dexamethasone (40 mg/day). At presentation, he was febrile (T-max, 38.6°C) with hyperbilirubinemia (peak total/direct bilirubin 4.4/3.3 g/dl) and elevated alkaline phosphatase (190 U/l), AST (145 U/l), and ALT (139 U/l). He also had evidence of acute on chronic renal impairment (peak creatinine of 3.4 mg/dl with baseline of 1.7 mg/dl). Except for fever, there was no evidence of systemic infection (normal vital signs and white blood count). Serology for acute viral hepatitis (HAV, HBV, and HCV) was negative. Abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) revealed no abnormalities. Hepatobiliary scan showed no evidence of acute cholecystitis. The patient’s home medications included hydralazine (25 mg/day) for the past 3 years and nitrofurantoin (100 mg/twice daily, given prophylactically for history of prior urinary tract infections) for the past 7 months, both of which rarely cause liver function impairment (3, 4). Both of these medications were continued during current admission since he had been on them chronically. Lenalidomide was stopped as it was
considered a potential cause of the acute liver injury. Hyperbilirubinemia subsequently normalized over four days and the other liver function tests also corrected within 8 days of lenalidomide discontinuation. The patient improved clinically, with resolution of symptoms, allowing for hospital discharge. Urinary tract infection was diagnosed (positive urinalysis, Escherichia coli isolated in urine culture) and was deemed to have caused the fever (resolved rapidly with cefepime). Renal impairment corrected to baseline with hydration and antibiotics. Co-incidence of liver function impairment with lenalidomide treatment and discontinuation suggested hepatotoxicity related to this medication. A RUCAM causality assessment score was 8 which is consistent with probable lenalidomide-associated hepatotoxicity (5).

Discussion

Patients with MM may develop hepatic abnormalities due to a multitude of causes. Consecutive case series demonstrate that in addition to reactivation of dormant chronic HBV infection while receiving chemotherapy, MM patients may develop amyloid infiltration of the liver, extramedullary plasmacytomas involving the liver, extramedullary hematopoiesis, and either vascular inflow or outflow complications (6-8). The latter is particularly important for knowledge for when using lenalidomide since it is associated with a >10% rate of thrombosis and prophylactic anticoagulation is recommended (9). Besides the current report, there are four published cases of lenalidomide-associated hepatotoxicity (Table I). One patient presented with predominant cholestasis (10), another patient had lenalidomide-associated hepatitis (11), the third patient had a mixed pattern of liver injury (12), and the fourth patient had asymptomatic elevation in serum aminotransferase levels (13). Three of the five reported patients had pre-existing renal insufficiency. Patients with reduced renal function (e.g. one third of patients with multiple myeloma) may be more prone to developing hepatotoxicity from lenalidomide as it is mainly excreted by the kidneys. Interestingly, the only patient that developed overt liver failure was receiving a renally-corrected lenalidomide dose (12). This patient had pre-existing chronic HBV infection and while on lenalidomide, he developed marked elevation of serum aminotransferase levels with hyperbilirubinemia, attributed to reactivation of hepatitis B, possibly induced by lenalidomide. In all cases, the timing of hepatic injury correlated with initiation of lenalidomide. Discontinuation of lenalidomide after liver impairment resulted in clinical and laboratory improvement in all patients with a mean time for LFT normalization of 21 days (range 8-30 days). The patient with acute liver failure also improved with supportive therapy within four weeks after lenalidomide discontinuation. Notably, two of the patients were re-challenged with low-dose lenalidomide after resolution of the hepatotoxicity which resulted in recurrence of liver biochemical abnormalities in one patient (3), and no hepatotoxic effect in another (12).

The mechanism of lenalidomide-associated hepatotoxicity remains unclear. Only two of the reported cases underwent liver biopsy: one showed lesions consistent with drug-induced liver injury (11), and the other demonstrated “non-specific” features (13).

Table I. Clinical characteristics of patients with lenalidomide-associated hepatotoxicity.

<table>
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<tbody>
<tr>
<td>Indication for lenalidomide therapy</td>
<td>MM</td>
<td>MM (lumbar spine lesions)</td>
<td>MDS</td>
<td>MM</td>
</tr>
<tr>
<td>Lenalidomide dose (mg/day)</td>
<td>25</td>
<td>10</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Length of therapy prior to liver injury (in days)</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>Not reported</td>
</tr>
<tr>
<td>Peak AP (u/l)</td>
<td>330</td>
<td>198</td>
<td>342</td>
<td>N/A</td>
</tr>
<tr>
<td>Peak AST/ALT (u/l)</td>
<td>70/100</td>
<td>246/509</td>
<td>1880/2670</td>
<td>Grade 2***</td>
</tr>
<tr>
<td>Peak bilirubin (mg/dl)</td>
<td>7</td>
<td>Normal</td>
<td>9.2</td>
<td>Unknown</td>
</tr>
<tr>
<td>RUCAM score†</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>N/A</td>
</tr>
<tr>
<td>Other patients’ characteristics</td>
<td>Renal insufficiency, prior chemotherapy and autologous stem cell transplant, liver biopsy*</td>
<td>Renal insufficiency, prior chemotherapy and allogeneic stem cell transplant, IgM anti-HBc all positive, HBV-DNA load &lt;26.6 copies/ml</td>
<td>Liver biopsy***, recurrent liver enzymes elevation when re-challenged</td>
<td>Renal insufficiency, prior chemotherapy and autologous stem cell transplant</td>
</tr>
</tbody>
</table>

† RUCAM score cut-off points include: ≤0 Excluded ADR ‡, 1-2 Unlikely ADR ‡, 3-5 Possible ADR ‡, 6-8 Probable ADR ‡, ≥9 Highly probable ADR. *Liver biopsy findings: prominent portal and lobular inflammation, mixed cellular infiltrate, rich in polynuclear eosinophils, lobular areas of confluent necrosis, mild lesions of endothelitis, occasional biliary cell dystrophy in some portal tracts. **Grade 2=2.6-5 x upper limit of normal AST/ALT. ***Liver histology findings reported as “non-specific”. MM – multiple myeloma, MDS – myelodisplastic syndrome, RUCAM - Roussel Uclaf Causality Assessment Method, ADR – adverse drug reaction, N/A – not applicable.
In summary, these data suggest that lenalidomide-induced liver injury can present with either an acute hepatocellular or cholestatic liver injury profile and varying histopathological features, usually during the first or second course of therapy. In the limited cases reported, lenalidomide hepatotoxicity appears to be reversible after drug discontinuation and is frequently associated with renal impairment. Physicians should be aware of this potential association given the increased frequency of lenalidomide usage.

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**References**


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