Resolution of Pruritus in association with treatment of chronic hepatitis c in an elderly man

Case report

A 79 year old man was referred to the hepatology clinic because of chronic hepatitis C virus (HCV) infection diagnosed at the time of the referral. He did not report any risk factors for infection. He did not have comorbidities and was not on any medications. The patient reported generalized pruritus. On exam he had cutaneous stigmata of chronic liver disease. Baseline laboratory exam results, depicted on the table, suggested advanced liver disease. Liver disease work up was noncontributory. An upper endoscopy revealed small esophageal varices. A liver sonogram was normal. Consistent with the stage of his disease (Table 1), cholestasis was considered to be a major contributing factor to his pruritus; thus, the patient was treated with cholestyramine, which he did not tolerate because of bloating, and with the antidepressant sertraline, which was not associated with relief. The opiate antagonist naltrexone was not prescribed because the patient did not want to take the risk of a potential opioid-withdrawal like reaction. During this time, the treatment of chronic HCV included pegylated interferon, thus, we were reluctant to treat him because of the side effects considering his age, and because he had had difficulties attending the clinic, which posed problems for follow up.

Table 1 Clinical data at baseline and follow up

<table>
<thead>
<tr>
<th>Test (normal range)</th>
<th>Baseline</th>
<th>Before treatment</th>
<th>At the end of 12 weeks of treatment</th>
<th>One year post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL) (3-5)</td>
<td>3.5</td>
<td>3.6</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>AST (0-40)/ALT(0-45) (U/L)</td>
<td>100/74</td>
<td>90/72</td>
<td>24/13</td>
<td>20/28</td>
</tr>
<tr>
<td>Alkaline phosphatase (30-120) (U/L)</td>
<td>130</td>
<td>123</td>
<td>114</td>
<td>83</td>
</tr>
<tr>
<td>Platelets (130-400) (U/L)</td>
<td>98</td>
<td>178</td>
<td>171</td>
<td>158</td>
</tr>
<tr>
<td>PT (9.5-11.8)/INR(0.8-1.2)</td>
<td>13.1/1.25</td>
<td>11.9/1.14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fibro test*</td>
<td>NA</td>
<td>F4 (Severe fibrosis)</td>
<td>NA</td>
<td>F4 (Severe fibrosis)</td>
</tr>
<tr>
<td>Acti test*</td>
<td>NA</td>
<td>A2-A3 (significant activity)</td>
<td>NA</td>
<td>A0</td>
</tr>
<tr>
<td>HCV RNA (IU/ml)</td>
<td>349,927</td>
<td>778,498</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Bilirubin (0-1.5) (mg/dL)</td>
<td>1.2</td>
<td>1.2</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Total fasting Bile acids μmol/L(&lt;6.8)</td>
<td>33.5</td>
<td>9.7</td>
<td>6.8</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*Liver fibrosis. Fibrotest™, Actitest™ panel, Quest diagnostics
NA: not available.
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Two years after the initial evaluation, he reported severe generalized pruritus associated with sleep deprivation; in addition, he said that one year prior to the visit he had developed a rash after admission to the hospital for treatment of spontaneous pneumothorax. On physical exam, he appeared his stated age, and had normal cognition. He had spider angiomata and a maculopapular rash on the chest, and generalized excoriations. The dermatologists opined that the pruritus was from chronic HCV; they did not document a rash, suggesting that it had resolved itself by the time the patient was seen. Their treatment with local therapy was not associated with relief of the symptom.

When sofosbuvir/ledipasvir (Harvoni ®) was approved for treatment of chronic HCV, the patient was started on a planned course of twelve weeks. Within four weeks of treatment, he reported that the pruritus had decreased and by week eight it had disappeared. He achieved SVR and has remained asymptomatic for over two years of follow up post treatment. His synthetic hepatic function has been normal (Table), and he has not developed hepatocellular carcinoma for which he accepted screening because he would want to be treated were it to develop; however, he has declined follow up endoscopy for evaluation of esophageal varices.

Discussion

This case is that of a man who suffered from pruritus in association with advanced liver disease from chronic HCV infection and a rash, which also might have been due to the viral infection but which seems to have spontaneously disappeared. The cure of his chronic HCV was associated with disappearance of his pruritus, normalization of serum activity of transaminases, and a gradual decrease of serum concentration of bile acids to normal ranges, the latter suggesting that the degree of cholestasis had also decreased.

Cholestasis is defined as impaired secretion of bile and is characterized by tissue accumulation of substances that are excreted in bile under physiological conditions including bile acids, cholesterol, and bilirubin. Pruritus is a complication of cholestasis; it is more common in conditions characterized by bile duct inflammatory destruction and ductopenia including primary biliary cholangitis (PBC); than in those characterized by hepatocellular disease including viral hepatitis; however, it can be as devastating as in cholestatic liver diseases, as described in the case above.

It is hypothesized that increased opioidergic tone contributes to the pruritus of cholestasis; other neurotransmitter systems including the serotonergic system may be involved. A role of bile acids and autotaxin has been proposed in the mediation of this type of pruritus; however, the endogenous opioid system may be the ultimate mediator of the pruritus, as it also has been hypothesized.

Pruritus was the presenting dominant symptom in four percent of patients with chronic HCV referred for treatment to a tertiary referral research institute in the United States; considering the high prevalence of chronic HCV worldwide1 pruritus is expected to be a prominent symptom in patients with this disease. This idea is supported by the results of a retrospective study from a center in Europe, which was reported to reveal that 40% of the patients with chronic pruritus from liver disease had chronic viral hepatitis B or C.

A retrospective study examined the histological features of patients with chronic HCV and pruritus, with PBC and pruritus and with chronic HCV without pruritus, the latter two as control groups. The eight patients with chronic HCV and pruritus had significant liver injury that included advanced fibrosis, severe inflammatory activity and cirrhosis in most cases, bile duct injury, bile ductular proliferation, and ductopenia; in addition, serum fasting cholyglycine levels were high in seven of the eight patients consistent with cholestasis. The group of eight patients with PBC exhibited marked ductopenia, and bile ductular proliferation, typical of this disease. However, in the disease control group, comprised of seven patients with chronic HCV without pruritus, only two had some degree of ductopenia, and one had bile ductular proliferation. These findings support the idea that in chronic HCV, pruritus tends to correlate with advanced liver disease, also supported by a study that reported that high liver stiffness predicts the development of pruritus in patients treated for HCV, and suggested by the findings in our patient who had stage 4 fibrosis and marked inflammatory activity by the fibrosure test, and cholestasis, suggested by increased serum concentrations of bile acids, as also recently reported from a study from the Middle East in patients with chronic HCV with pruritus versus those without this symptom.

Descriptions of the sensation of pruritus by patients with liver disease including PBC, cholestatic drug-induced liver injury, and viral hepatitis tend to be similar, i.e. generalized, “pins and needles”, “under the skin”, not relieved easily by scratching, and worse from the late afternoon and evening (NVBergasa, personal observations 1988 - 2018) suggesting that the manner in which the pruritus is perceived does not depend on the cause of the liver disease and that the mechanism that mediates the pruritus is the same. In this regard, we suggest that the stratification of results from clinical trials of drugs for pruritus in patients with liver disease according to their etiology may help to identify potential differences or confirm similarities.

HCV infection has been reported in association with several dermatological conditions including bullous pemphigoid and lichen planus; however, these diseases have typical skin findings that the patient described here did not have. The rash that he developed might have been due to chronic HCV, however, as it disappeared spontaneously, we cannot comment on any potential effects of treatment on it.

The relatively rapid manner in which the pruritus ceased during HCV treatment merits discussion. Although fibrosis regresses after association with SVR it does it relatively slowly, i.e. the time for pruritus relief may be expected to be longer than what was reported by the patient if it was all related to fibrosis and cirrhosis; on the other hand, as assessed by serum bile acids, the degree of cholestasis decreased, suggesting that there was an effect of the treatment on the mechanism that perpetuates it. It is also possible that the diminution of inflammatory activity, as suggested by the marked decrease in serum activity of transaminases early in the treatment, was sufficient to decrease the degree of cholestasis, not reaching the threshold at which pruritus was perceived by the patient. This observation may be analogous to the severe pruritus experienced by some patients with Stage I PBC who have the florid bile duct lesion, characterized by a rich inflammatory attack on bile ducts and no fibrosis, suggesting that inflammation may contribute to the pathogenesis of the pruritus of cholestasis.

Conclusion

In summary, pruritus has a tremendously negative impact on the quality of life of patients; accordingly, in patients with HCV it is an

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indication for prompt treatment and as important as complications of renal disease and cryoglobulinemia, regardless of the patient’s age and comorbidities.

Acknowledgments
None.

Conflicts of interest
The author declares no conflicts of interest.

References