

## Autoimmune Hepatitis and Hypergammaglobulinemic Purpura Associated with Herbal Medicine Use

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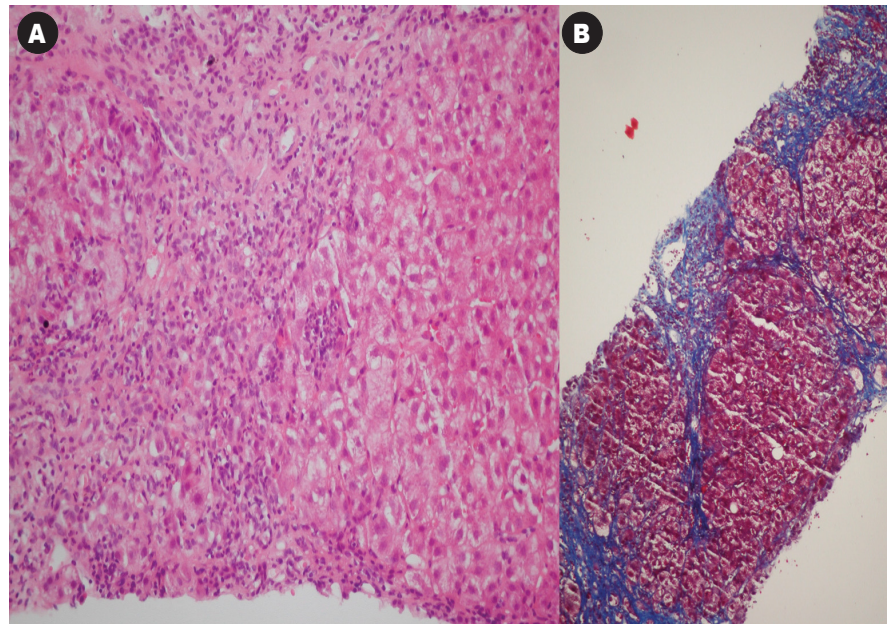
Autoimmune hepatitis is a chronic hepatitis of unknown etiology characterized by hyperglobulinemia, circulating antibodies and piecemeal necrosis on liver histology. There are only sporadic reports describing an association between autoimmune hepatitis and herbal medications [1]. Herbal remedies are among the most popular form of complementary treatments and are being marketed and used at an increasing rate [2]. We present, to the best of our knowledge for the first time, a patient with autoimmune hepatitis and hypergammaglobulinemic purpura related to herbal medicine that promptly responded to corticosteroid therapy.

### Patient Description

A 57 year old previously healthy woman, a practitioner of alternative medicine, was hospitalized with jaundice and weakness. One month prior to her current admission she became progressively weak, with jaundice appearing 2 weeks later. The patient does not take conventional medications but uses a variety of herbal preparations, including echinacea, kombucha, Chinese herbal mixtures and kava kava. She denied any history of blood transfusions, drug or alcohol use, or any known contact with hepatitis patients.

On physical examination she was afebrile, yet visibly jaundiced, with no apparent distress. The abdomen was soft with mild right upper quadrant tenderness. The liver span measured 15 cm and the spleen was not palpable. There were no signs of encephalopathy, rash or peripheral edema.

The laboratory data revealed hemoglobin 11.6 g/dl, platelets 147,000/ $\mu$ l,



Liver biopsy showing [A] piecemeal necrosis (hematoxylin & eosin stain), [B] cirrhotic nodules (Masson stain)

international normalized ratio 1.83, total bilirubin 12.1 mg/dl (direct bilirubin 9.1 mg/dl), alkaline phosphatase 100, aspartate aminotransferase 1483, alanine aminotransferase 862, serum globulin 7.2 g/dl, serum albumin 3.7 g/dl; immunoglobulin levels were IgG 39,100 mg/dl, IgA 317 mg/dl, IgM 107 mg/dl; antinuclear antibody peripheral pattern +4 and anti-DNA tests and rheumatoid factor were positive. Anti-smooth muscle antibodies were positive while anti-mitochondrial antibodies, anti-liver-kidney-microsomal antibodies were negative, and C3, C4 complement levels were within normal range. Viral serology for hepatitis B and C were negative. Cytomegalovirus and Epstein-Barr virus IgM tests were negative,

while IgG tests were positive. Abdominal ultrasound and computed tomography were normal. A liver biopsy demonstrated cirrhosis with severe piecemeal necrosis, severe intra-acinar necrosis, focal necrosis and cholestasis [Figure]. These findings were consistent with a diagnosis of autoimmune hepatitis and cholestasis.

The patient was started on prednisone 60 mg per day with a prompt clinical and laboratory improvement. On the eleventh day of hospitalization skin purpura appeared and a skin biopsy demonstrated extravasation of erythrocytes in the upper dermis without evidence of vasculitis (histologically confirmed purpura). The patient was discharged from the hospital on day 19, with complete normalization

of her liver function. One month after discharge she decided to stop steroid therapy and resume the herbal medications. Laboratory tests showed renewed elevation of transaminases and bilirubin levels shortly after the intentional challenge by the patient.

### Comment

To the best of our knowledge this is the first report of autoimmune hepatitis combined with hypergammaglobulinemic purpura associated with herbal medicine use. In 1950 Waldenstrom was the first to report chronic hepatitis in a young woman with cirrhosis, liver plasma cell infiltration and hypergammaglobulinemia. Many terms have been used to describe this clinical entity, such as lupoid hepatitis and plasma cell hepatitis, but in 1992 an international group recommended the term Autoimmune Hepatitis. It is well known that herbal medications can cause hepatitis and even lead to fulminant hepatic failure. Herbal use is often not disclosed, and this may result in a diagnostic delay and exacerbation of liver injury. Female gender may predispose to hepatotoxicity, and concomitant agents that induce cytochrome P450 enzymes may also increase an individual's susceptibility. The range of liver injury includes minor transaminase elevations, acute and chronic hepatitis, steatosis, cholestasis, zonal or diffuse hepatic necrosis, hepatic fibrosis and cirrhosis, veno-occlusive disease, and

acute liver failure requiring transplantation [3]. The most common herbal remedies implicated include: echinacea, combucha, Chinese herbal mixtures, kava kava – all of which our patient was using repeatedly. There are only sporadic previous reports of an association of AIH and herbal medications [1]. It remains speculative whether this association is causative or merely coincidental. Alternatively, herbal remedies may act as a trigger for an immune process ultimately resulting in AIH. Cholestatic pathological findings can occur in classic AIH regardless of clinical cholestasis, and typically they do not affect prognosis or treatment response. In addition, certain herbal remedies are capable of inducing hepatitis with a cholestatic pattern. For example, the Chinese herbal medicine syo-saiko-to may induce acute injury or a hepatocellular injury pattern with variable cholestasis [4]. The diversity of histological findings in the current case may have been related to the multifactorial etiology of our patient's liver injury, i.e., AIH type I and toxic hepatitis due to herbal medicine. An additional distinctive feature of the case under discussion is non-thrombocytopenic purpura. Few cases of purpura in association with AIH have been reported [5]. The mechanism of this association is unknown and is assumed to be related to hypergammaglobulinemia, which was also found in our

AIH = autoimmune hepatitis

patient. Waldenstrom was also the first to describe, in 1943, an association between hypergammaglobulinemia and purpura. The combination of AIH, herbal medication use and hypergammaglobulinemic purpura has not been reported previously.

In summary, AIH and purpura may be related to herbal medications. This recognition is important as this entity promptly responds to steroid therapy. Since the use of herbal medicines is increasing worldwide, this association may become increasingly more frequent.

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