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Single Case

Secondary Adrenal Insufficiency after Treatment with Budesonide for Autoimmune Hepatitis

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Abstract
Autoimmune hepatitis (AIH) is a rare cause of chronic liver disease. The backbone of treatment is immunosuppressive medication, typically prednisolone as induction therapy and azathioprine as a maintenance therapy. Side effects of the long-term use of systemic corticosteroids are well known and have led to the use of alternative induction regimens. An attractive alternative is budesonide, a nonhalogenated glucocorticosteroid characterized by a high first-pass effect in the liver (90%), resulting in a high topical anti-inflammatory activity and a low systemic activity. It should be stressed that budesonide is contraindicated in patients with established cirrhosis with portal hypertension and portocaval shunting. In this case report, we present the first case of adrenal insufficiency following treatment with budesonide for AIH.

Introduction

Side effects of the long-term use of systemic corticosteroids are well known and have led to the use of alternative induction regimens. An attractive alternative is budesonide, a

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nonhalogenated glucocorticosteroid characterized by a high first-pass effect in the liver (90%), resulting in a high topical anti-inflammatory activity and a low systemic activity. The binding activity of budesonide to the glucocorticosteroid receptor is 15–20 times higher than that of prednisolone [1, 2]. Because of 90% inactivation in the liver, the systemic concentration is low, thus minimizing the effect on the hypothalamic-pituitary-adrenal axis. Due to its attractive safety profile, budesonide is now used as an alternative to prednisolone in the treatment of autoimmune hepatitis (AIH) in noncirrhotic patients [3]. It should be stressed that budesonide is contraindicated for patients with established cirrhosis with portal hypertension and portocaval shunting. Portal venous thrombosis has been reported in 2 patients with primary biliary cholangitis (PBC) stage IV treated with budesonide and ursodeoxycholic acid [4]. In this case report, we present the first case of adrenal insufficiency following treatment with budesonide for AIH.

AIH is a rare chronic liver disease with an estimated prevalence of 15–25 per 100,000. Its prevalence may vary according to ethnicity and seems to be increasing. The time of presentation is bimodal, resulting in a first peak in childhood/teenage years and a second peak between the 4th and 6th decades. Predominantly women are affected [5].

Its main features are hypergammaglobulinemia (IgG), typical histological findings on liver biopsy (Fig. 1), and response to immunosuppression. If left untreated, this condition can rapidly progress to cirrhosis, finally resulting in liver failure and death. Its diagnosis can be challenging due to the heterogeneity of clinical symptoms and presentation. The spectrum of presentation ranges from asymptomatic to acute and severe hepatitis, sometimes resulting in liver failure. Most frequently, as seen in two-thirds of cases, patients present with an insidious onset without apparent symptoms or vague and general symptoms like fatigue, general feeling of illness, lethargy, and anorexia. Because of the quiescent course, one-third of patients will already have developed cirrhosis at the time of diagnosis. In about one-quarter of patients, an acute hepatitis (true or exacerbation of a chronic form) is seen at presentation.

A typical but nonspecific finding is a rise in aminotransferases. Cholestatic liver enzymes are usually normal or only slightly elevated (only GGT, not ALP). Furthermore, IgG levels are typically elevated and autoantibodies are the hallmark of the disease, leading to a subclassification into three categories. The first type, AIH 1, is most common (90%). In this type, antineutrophil antibodies (ANA) and/or smooth muscle antibodies or anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP) are detected. The second type, AIH 2, accounts for about 10% of cases. This subtype is characterized by detection of liver kidney microsomal antibodies (anti-LKM1) or anti-LKM3 and/or liver cytosol type 1 antibodies (anti-LC1). AIH 3 is quite rare and is characterized by the detection of anti-SLA/LP and often Ro-52 antibodies.

For induction of remission, patients are classically treated with corticosteroids, typically high-dose prednisolone. A combination with azathioprine is effective and reduces the corticoids' systemic adverse effects by reducing the dose of corticosteroids needed for remission. After achievement of remission, the corticosteroids are gradually tapered. An alternative corticosteroid is budesonide, characterized by a high first-pass effect in the liver (90%), resulting in a high topical anti-inflammatory activity and a low systemic activity, limiting any adverse effects. Contraindications are portal hypertension (cirrhosis) or portocaval shunts, because of strong systemic adverse effects in these cases.

Case

A 39-year-old female without a prior medical history was referred by the general practitioner for complaints of fatigue and elevated liver enzymes (AST/ALT 412/547 U/L, GGT 104 U/L, AF 81 U/L, and bilirubin 1.5 mg/dL). Her further history was unremarkable. There were neither complaints of abdominal pain nor nausea or vomiting. Stool consistency and frequency remained normal. Neither blood in the stool nor discoloration (black or pale) was seen. She had no fever, night sweats, or weight loss. No complaints of palpitations, thoracic pain, dyspnea, orthopnea, or cough were reported. Semi-recent intake of antibiotics or other hepatotoxic drugs was denied by the patient. Her family history regarding liver or autoimmune diseases was negative.

A complete blood analysis was performed and showed no anemia, no thrombopenia, and no signs of inflammation. Thyroid function tests seemed normal. Kidney function tests also appeared normal; only liver tests were augmented as already stated earlier. Ferritin, copper, and ceruloplasmin were normal. Results of initial IgA, IgM, and IgG were not found. Viral serology (CMV, toxoplasmosis, HAV, HBV, HCV, and HEV) remained negative, and immunity against EBV was acquired. Also, autoimmune testing (ANA, anti-AMA, anti-LKM, and anti-LC1) proved negative. Echography of the abdomen showed no abnormalities. Because neither biochemistry nor echography revealed an evident cause, a liver biopsy was performed. An image of chronic hepatitis with mild fibrosis and high inflammatory activity (A3F2) combined with infiltration of plasmacytes and eosinophils was observed (Fig. 1). This was suggestive of AIH, possibly drug induced.

Treatment with budesonide 9 mg was started, with good response initially. Upon tapering of budesonide after 2 months, the patient showed clinical signs of relapse. Therefore, azathioprine was added. Hereafter, transaminases returned to normal levels. However, the patient was still not feeling well, with persistent complaints of fatigue. Treatment with azathioprine was stopped because concerns arose that the fatigue might be a side effect of this treatment. Three months later, the fatigue had increased. Furthermore, the patient reported, for the first time, concentration disorders, muscle weakness, weight loss, orthostatism, and amenorrhea. At this time, endocrinologic testing was performed. We saw a normal thyroid gland function, but early-morning plasma cortisol values were significantly decreased (18.8 μg/L; reference: 67–226), which was concordant with a low urinary cortisol level (12.0 μg/24 h urine; reference 36–137) and decreased ACTH (<5.0 ng/L).

Budesonide treatment was stopped, and adrenal substitution with hydrocortisone (20 mg – 5 mg – 10 g) was started. After 2 months of treatment, an improved morning cortisol level (69.3 μg/L) was observed. Hydrocortisone was gradually tapered. However, ACTH remained low (<5.0 ng/L). Thus, a Synacthen test was performed to investigate the reactivity of the adrenal gland. Cortisol levels at 30, 60, and 90 min were 66.1, 73.9, and 72.8 μg/L, respectively, showing insufficient adrenal recuperation at that moment. Hydrocortisone treatment needed to be continued and was, later on, gradually tapered. Liver function tests remained normal.

Discussion

Only a few cases of adrenal insufficiency caused by budesonide have been reported. These reports involved patients treated with budesonide for Crohn's disease or asthma [6]. Pharmacokinetic and pharmacodynamic analysis of budesonide 9 mg treatment for 3 weeks in 19

patients with PBC showed significantly lower morning plasma cortisol and urinary cortisol levels in late-stage PBC (cirrhosis) compared with early-stage PBC [4]. This underlines the importance of normal liver function to limit the systemic effects of budesonide. A decreased liver function presents as lowered albumin, elevated bilirubin, and lowered prothrombin time and results in a higher systemic budesonide concentration. In the presence of portal hypertension and portocaval shunting, as seen in cirrhosis, the systemic concentration of budesonide is even higher.

The patient in this case, however, had a normal liver function without signs of cirrhosis on liver biopsy. Only mild fibrosis was reported. Furthermore, there were no signs of portal hypertension or shunting. No specific medications affecting the hypothalamic-pituitary-adrenal axis, excluding budesonide, were ingested during this period, nor did the patient take any medications which influenced CYP3A4, needed for metabolism of budesonide. The patient only intermittently used vaginal creme containing isoconazole (Travocort®). Ketoconazoles inhibit CYP3A4, but the systemic effects of local use are unlikely to be significant.

We conclude that this patient with AIH developed iatrogenic adrenal insufficiency following oral budesonide treatment. Although it is an attractive treatment strategy for AIH patients without cirrhosis, caution is advised for persistent, vague symptoms which could reflect adrenal insufficiency. Simultaneous intake of other drugs affecting CYP3A4 should be taken into account and should better be avoided.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

There are no conflicts of interest.

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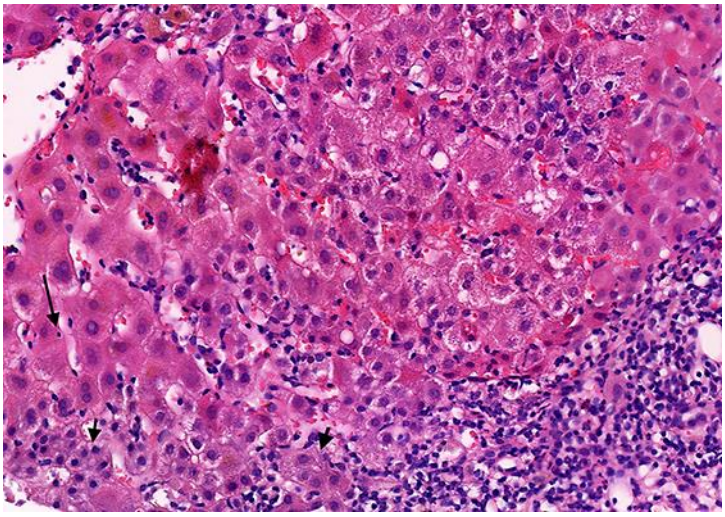

Fig. 1. Liver biopsy showed a chronic hepatitis-like injury with an intense mixed portal and periportal inflammation composed mainly of lymphocytes and macrophages, accompanied by some eosinophils. There was no profusion of plasma cells. Interface hepatitis was marked and was associated with periportal fibrosis. There was also lobular inflammation with spotty necrosis and apoptosis. The short arrows point to hepatic rosette formation; the long arrow points to a focus of emperipolesis. Hematoxylin-eosin stain. Magnification, ×250.