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CASE REPORT

Hepatocellular carcinoma after danazol treatment for hereditary angio-oedema

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ABSTRACT

Hereditary angio-oedema is characterised by recurrent episodes of laryngeal, intra-abdominal, facial or peripheral oedema. Danazol can be used as prophylaxis for recurrent attacks. Hepatotoxicity is a recognised adverse effect of danazol. We report an exceptional case of a danazol-induced hepatocellular carcinoma in a 75-year-old patient with hereditary angio-oedema.

KEYWORDS

Hepatocellular carcinoma, HCC, danazol, hereditary angio-oedema, androgen therapy

What was known on this topic?
In the literature, only two cases of a danazol-induced hepatocellular carcinoma (HCC) in patients with hereditary angio-oedema have been described. HCC as a result of danazol has also been reported in patients with idiopathic thrombocytopenic purpura and systemic lupus erythematosus. We know that patients with an increased risk of HCC (such as patients with chronic hepatitis B and cirrhosis), should have an ultrasound of the liver every six months according to the Dutch HCC guideline. Chronic danazol use is not mentioned as an increased risk factor for HCC.

What does this add?
HCC is a rare side effect of long-term danazol treatment in patients with hereditary angio-oedema. This case report illustrates the importance of ultrasound monitoring of the liver in patients on long-term danazol treatment. Our suggestion is to add chronic danazol use to the increased risk group in the Dutch guideline for HCC, which implies that these patients should have an ultrasound of the liver every six months.

INTRODUCTION

Hereditary angio-oedema is a potentially life-threatening disease and is characterised by recurrent episodes of laryngeal, intra-abdominal, facial or peripheral oedema.[1] Hereditary angio-oedema is caused by a deficiency or dysfunction of the C1 inhibitor.[1] Danazol can be used as long-term prophylaxis to prevent recurrent attacks of hereditary angio-oedema.[1] Hepatotoxicity is a recognised adverse effect of danazol, which can result in hepatitis with hepatocellular necrosis, cholestasis, and the development of adenomas, focal nodular hyperplasia and rarely hepatocellular carcinoma (HCC).[1,2] We report a patient with hereditary angio-oedema on long-term prophylaxis with danazol, who developed HCC.

CASE REPORT

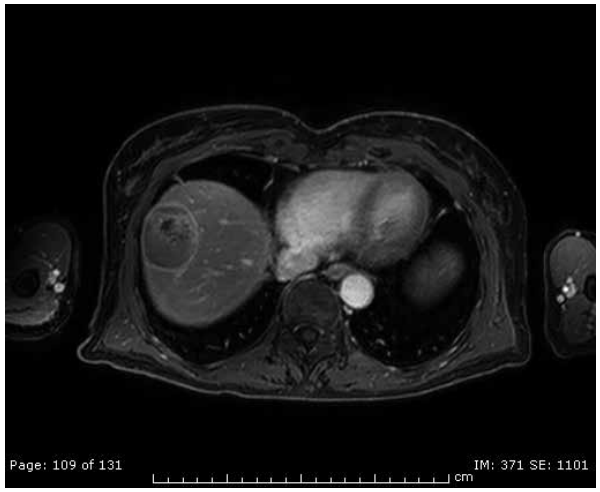
A 75-year-old woman, with a history of hereditary angio-oedema, was referred by her general practitioner to the emergency department because of pain in the right upper abdomen. The pain had existed for one day. She was on danazol 300 mg (accidental 400 mg) once daily for 33 years. She underwent annual liver ultrasound because of the (rare) risk of the development of a danazol-induced adenoma or HCC. The last ultrasound (nine months ago) showed gallbladder sludge, but no liver abnormalities.

On physical examination we saw a non-ill patient with tenderness in her right upper abdomen. Laboratory tests showed a slightly elevated aspartate aminotransferase and alanine aminotransferase. Ultrasound of the abdomen showed gallbladder sludge and a hyperechoic lesion with a hypoechoic rim of 4 x 4 cm in segment VIII of the liver. Additional blood tests (hepatitis A, B, C serology, alpha-fetoprotein) and an MRI of the liver were requested, because of the suspicion of HCC. Hepatitis serology was negative and alpha-fetoprotein was normal (2.90 μg/l; reference: < 20 μg/l). MRI showed a lesion of 4.1 x 4.6 x 4.2 cm in segment VIII of the liver with bulging of the liver capsule, without invasion in the vessels. The mass was slightly hyperintense on the T2-weighted sequences with centrally a few foci with varying intensity. After administration of contrast, we saw a heterogeneous enhancement in the arterial phase, with wash-out in the portal venous phase. In the late phase, there was capsular enhancement (*figure 1*), very suspect for HCC. There were no other suspicious lesions or signs of cirrhosis.

Resection of segment VIII and gallbladder (because of sludge) was performed. Danazol was stopped and patient was given an injection of Cynrize, a plasma-derived human C1 inhibitor, every three days to prevent perioperative angio-oedema. Pathological examination confirmed the diagnosis of HCC in a non-cirrhotic liver, which was radically removed.

The postoperative course was complicated by a subphrenic abscess, which was drained percutaneously. Hereafter, she recovered quickly. Remarkably, the patient had only minimal symptoms of angio-oedema in the four months after surgery, without medication.

Figure 1. *Axial T1-weighted magnetic resonance image (MRI) of the tumour in segment VIII of the liver with fat suppression in the late phase after intravenous contrast. There is a capricious staining and capsule visible around the central necrosis*



DISCUSSION

HCC is a rare side effect of long-term danazol treatment in patients with hereditary angio-oedema. The much commoner causes of HCC, such as cirrhosis and viral hepatitis, should be excluded first. This case illustrates the importance of ultrasound monitoring of the liver in patients on long-term danazol treatment.

Hereditary angio-oedema

Hereditary angio-oedema is an autosomal dominant disease, caused by mutations in the gene coding for C1 inhibitor located on chromosome 11. The incidence of hereditary angio-oedema is approximately 1:50,000.[3] There are two classical types of hereditary angio-oedema that result from deficiency (type I, 85%) or dysfunction (type II, 15%) of the C1 inhibitor, which results in excessive production of bradykinin (vasodilatory mediator).[1,3] The disease is characterised by recurrent episodes of angio-oedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts.[1,3]

Danazol

Nearly all affected patients with hereditary angio-oedema are heterozygotes, which means that stimulation of the proper functioning gene can result in higher concentrations of C1 inhibitor. Such an effect can be achieved with the attenuated androgen danazol, the most frequently used long-term prophylactic agent in the treatment of hereditary angio-oedema.[1] Danazol is also used in the treatment of endometriosis, benign fibrocystic breast disease, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus.[1] Danazol was prescribed to 251 patients in the outpatient setting in the Netherlands in 2011.[4]

Described hepatotoxic side effects of danazol are hepatocellular necrosis, cholestasis, hepatocellular adenoma, focal nodular hyperplasia, and rarely HCC.[1,2] It is thought that androgens might have a direct mutagenic effect on the liver.[1] The magnitude of the risk of developing HCC from androgens cannot be determined, due to lack of data on this. The risk of developing hepatic adenomas in patients with hereditary angio-oedema on danazol is 7%, and the risk is about 26% if danazol is taken for more than ten years.[1] Malignant transformation is found in 4-16% of the adenomas;[5] however, there is also literature that suggests that malignant transformation of an adenoma is highly unlikely.[6]

In 1985, Buamah described a danazol-induced HCC for the first time, in a patient with endometriosis.[7] In the literature, two cases of a danazol-induced HCC in patients with hereditary angio-oedema have been described.[1,2] HCC as a result of danazol has also been reported in patients

with idiopathic thrombocytopenic purpura and systemic lupus erythematosis.[1]

Hepatocellular carcinoma

HCC is a primary tumour of the liver, which usually develops in the setting of chronic liver disease, particularly in patients with cirrhosis and/or viral hepatitis. In the absence of a surveillance program, HCC is frequently diagnosed late because of the absence of pathognomonic symptoms. Extrahepatic metastases are present at the time of the diagnosis in 5-15% of patients.[8,9] Resection of the HCC is the treatment of choice, but many patients are not eligible for resection because of extrahepatic metastases, anatomical constraints of the tumour, multifocal presence of the tumour, and/or poor underlying liver function.[10,11] Other curative treatment modalities are liver transplantation or radiofrequency ablation.[10,11] After curative treatment of HCC in a non-cirrhotic liver, as in this case, the three-year survival rate is 59%.[11] The presence of underlying cirrhosis is not associated with the survival rate and disease-free survival following potential curative treatment.[11] Recent work by Witjes *et al.* showed that immunohistochemical expression of several markers in HCC in a non-cirrhotic and cirrhotic liver was comparable.[12]

Follow-up

The international consensus meeting on hereditary angio-oedema[3] recommends annual liver ultrasound in patients on a daily danazol dose of 200 mg or less, and every six months in patients on doses higher than 200 mg. The patient in our case underwent annual liver ultrasound, whereas according to the consensus meeting biannual ultrasound was indicated. Patients with an increased risk of HCC, such as those with chronic hepatitis B and cirrhosis, should have an ultrasound of the liver every six months according to the Dutch guideline on HCC.[13] Chronic danazol use is not mentioned as an increased risk factor for HCC. Our suggestion is to add chronic danazol use to the increased risk group. In general, early detection of HCC is useful, because smaller tumours can be treated locally, and this increases the chance of survival.[13]

In conclusion, strict follow-up of patients on long-term danazol is recommended because of the risk of developing HCC. Diagnosis of danazol-induced HCC should be made after other causes such as cirrhosis and viral hepatitis have been excluded.

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DISCLOSURES

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