Case Report

Marked Transient Hypercholesterolemia Caused by Low-dose Mitotane as Adjuvant Chemotherapy for Adrenocortical Carcinoma

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We herein report a case of marked transient hypercholesterolemia in a man receiving low-dose mitotane as adjuvant chemotherapy for adrenocortical carcinoma.
A 58-year-old man without any clinical symptoms or history of hypercholesterolemia was admitted to our hospital to treat an adrenocortical carcinoma detected on general screening using computed tomography. He reported no chest symptom and did not exhibit any established risk factors for coronary artery disease, such as diabetes, obesity, hypertension or relevant family history, with the exception of current smoking, on admission. A stress electrocardiogram showed negative findings. The left adrenal tumor as well as left kidney, spleen and distal portion of the pancreas were subsequently resected using radical surgery. The histopathological findings confirmed the preoperative diagnosis of adrenocortical carcinoma. After the operation, treatment with low-dose mitotane (1g/day) was introduced as adjuvant chemotherapy. Interestingly, the patient developed marked hyper-LDL cholesterolemia at a level equivalent to that of familial hypercholesterolemia (LDL cholesterol level ~ 300 mg/dL) following the introduction of mitotane, without evidence of primary or secondary hypercholesterolemia due to other causes. A coronary angiogram performed to assess the new-onset angina revealed three-vessel disease, which was later revascularized via percutaneous coronary intervention eight months after the start of mitotane therapy. The cholesterol level normalized with the suspension of mitotane. This case suggests that mitotane can cause severe hypercholesterolemia, potentially resulting in coronary atherosclerosis.

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Key words: Mitotane, Adrenocortical carcinoma, LDL cholesterol, Familial hypercholesterolemia

Introduction

Adrenocortical carcinoma is a rare cancer (estimated incidence, 0.7 to 2.0 cases per 1 million population per year) that displays a poor response to cytotoxic treatment, with only 16% to 38% of patients surviving for more than five years after diagnosis[1]. As many as 75% to 85% of patients develop recurrence, even after radical resection[2, 3]. The high recurrence rate has motivated physicians to use adjuvant chemotherapy. Mitotane (a derivative of the insecticide dichlorodiphenyldichloroethane that specifically inhibits cells of the adrenal cortex and their production of hormones) has been widely applied for this purpose[4, 5]. However, limited data exist regarding the potential for secondary hypercholesterolemia caused by mitotane therapy.

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Case Report

A 58-year-old man without any clinical symp-

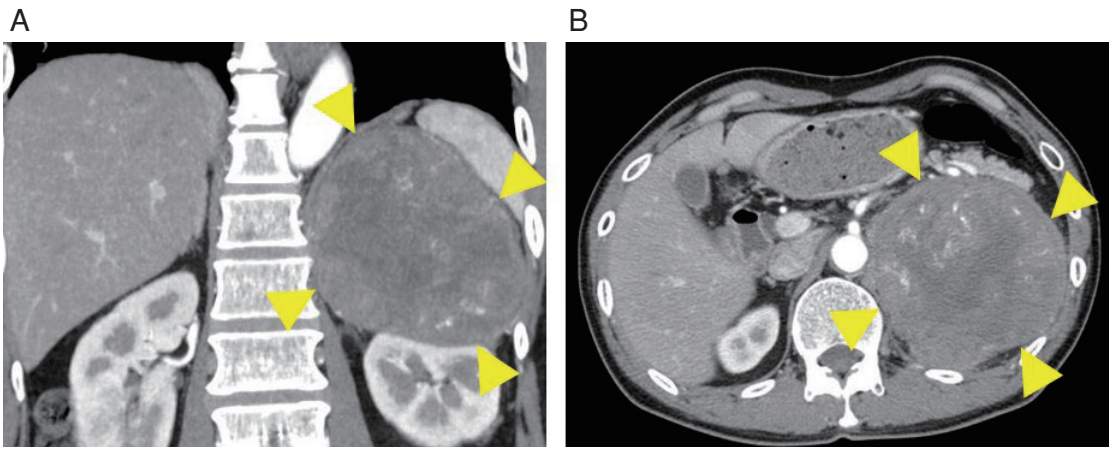

Fig. 1. Computed tomography.

Enhanced computed tomography performed on admission revealed a large tumor in the left adrenal gland (10 cm × 10 cm × 13 cm). (A) Coronal plane. (B) Transverse plane.

Table 1. Levels of intermediate metabolites of the biosynthesis of steroids before and after surgery

	DHEA-S (μg/dL)	Corticosterone (ng/mL)	DOC (ng/mL)	18-OH DOC (ng/mL)	Pregnenolone (ng/mL)
before	214	6.55	0.32	0.13	0.34
after	123	6.72	0.32	0.11	0.39

DHEA-S: dehydroepiandrosterone sulfate, DOC: 11-deoxycorticosterone, 18-OH DOC: 18-Hydroxy-11-deoxycorticosterone

toms or history of hypercholesterolemia with ApoE phenotype E3/E3 was admitted to our hospital to treat an adrenocortical carcinoma measuring 10 cm × 10 cm × 13 cm in size detected on general screening using computed tomography (**Fig. 1**). He reported no chest symptoms and did not exhibit any established risk factors for coronary artery disease, such as diabetes, obesity, hypertension or family history, with the exception of current smoking. A stress electrocardiogram showed negative findings at that time. The left adrenal tumor as well as left kidney, spleen and distal portion of the pancreas were successfully resected using radical surgery. The histopathological findings confirmed the preoperative diagnosis of adrenocortical carcinoma. We determined that the adrenocortical carcinoma to be nonfunctional, as no significant changes were observed in the levels of intermediate metabolites of the biosynthesis of steroids before and after the operation (**Table 1**). Treatment with low-dose mitotane (1 g/day) was introduced postoperatively as adjuvant chemotherapy, as recommended. Interestingly, the patient developed marked hyper-LDL cholesterolemia, the level of which was equivalent to that of familial hypercholesterolemia (LDL cholesterol level ~ 300 mg/dL) after the introduction of mitotane (**Fig. 2**). There was no family history of hypercholesterolemia or xanthomas. In addition, there was no evidence of secondary hypercholesterolemia due to other causes, such as hypothyroidism or other abnormalities on endocrinological examinations performed before and after surgery (**Table 2**). A coronary angiogram conducted to evaluate the new-onset angina revealed three-vessel disease, which was subsequently revascularized via percutaneous coronary intervention eight months after the introduction of mitotane, without any abnormal inflammatory reactions or other abnormal physical findings associated with vasculitis syndrome (**Fig. 3**). The cholesterol level normalized with the suspension of mitotane. There have been no obvious episodes of recurrence for at least five years after radical resection and the withdrawal of adjuvant mitotane chemotherapy.

Discussion

We experienced a unique case of "pseudo-familial hypercholesterolemia" caused by mitotane administered as adjuvant chemotherapy after radical resection

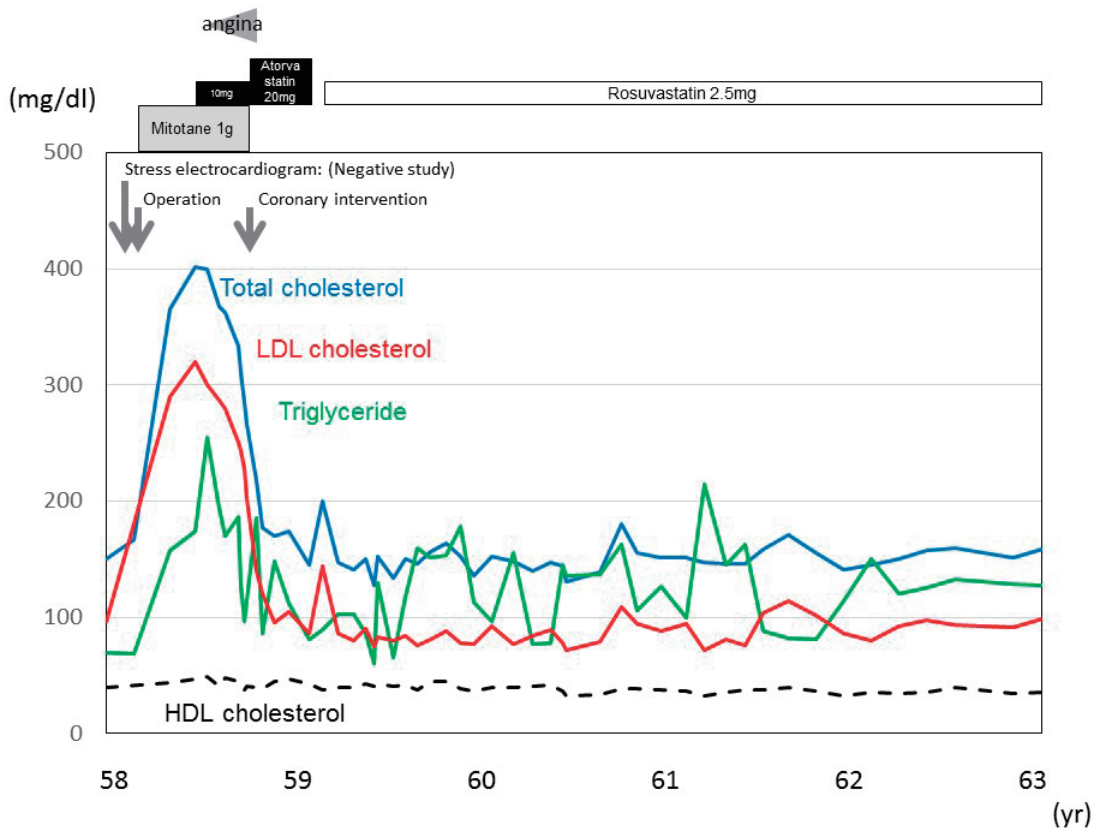

Fig. 2. Clinical course.

The solid blue line indicates the total cholesterol level (mg/dL). The solid red line indicates the LDL cholesterol level (mg/dL). The solid green line indicates the triglyceride level (mg/dL). The dotted black line indicates the HDL cholesterol level (mg/dL).

Table 2. Results of the endocrinological examinations before and after surgery

	FT3 (pg/mL)	FT4 (ng/dL)	TSH (μU/mL)	Cortisol (μg/dL)	Renin (ng/mL)	Aldosterone (pg/mL)	ACTH (pg/mL)	Epinephrine (pg/mL)	Norepinephrine (pg/mL)	Dopamine (pg/mL)
before	2.52	0.87	1.63	9.6	2.1	127	25.8	0.03	0.55	0.03
after	2.9	1.14	2.17	10.4	0.6	106	45.6	0.04	0.3	0.03

ACTH: Adrenocorticotropic hormone

of an adrenocortical carcinoma. Trainer P.J. *et al.* reported that, in their study, all 21 patients with Cushing's syndrome treated with mitotane exhibited increased cholesterol (primarily LDL cholesterol) levels, with an average of 68%[6]. We previously summarized possible mechanisms underlying the cholesterol-elevating effects of mitotane. First, mitotane may increase cholesterol synthesis by impairing the formation of oxysterol, which is responsible for downregulating hepatic cholesterol synthesis[7]. Second, mitotane may decrease cholesterol catabolism by inhibiting the production of cholesterol oxidase[8]. In accordance with these reports, treatment with a statin as well as the discontinuation of mitotane were effective in reducing the patient's serum cholesterol level in this case. Interestingly, our patient developed severe coronary atherosclerosis without any established risk factors for coronary artery disease, other than current smoking, including diabetes, obesity, hypertension and family history. In addition, a stress electrocardiogram performed prior to the initiation of mitotane revealed negative findings, suggesting that severe coro-

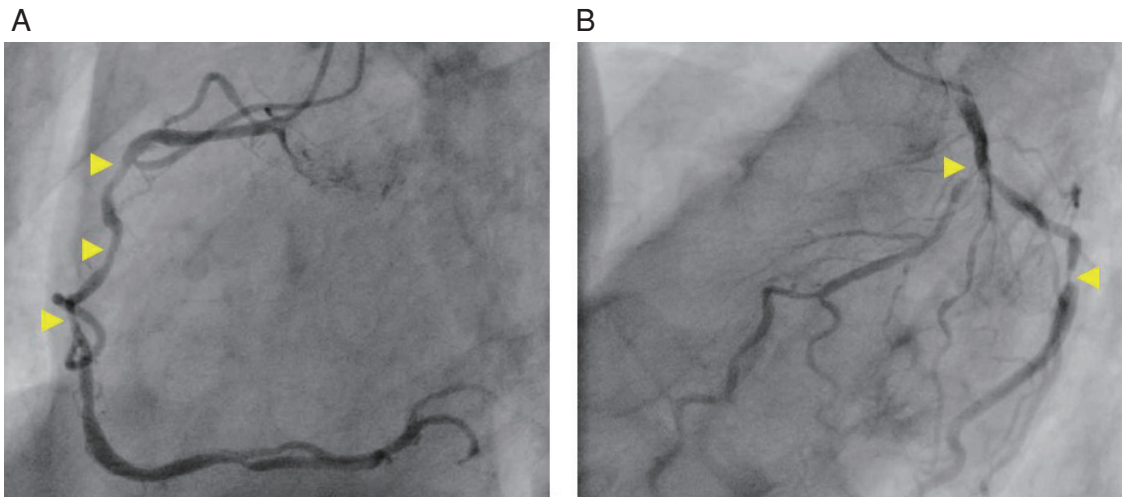

Fig. 3. Coronary angiogram.

(A) Tandem severe stenotic lesions were observed in the right coronary artery.
(B) Severe stenotic lesions were detected in the left anterior descending artery and left circumflex artery.

nary atherosclerosis may develop within a rather short period under conditions of extreme hyper-LDL cholesterolemia induced by mitotane. The publication of several papers describing infantile cases of homozygous familial hypercholesterolemia in patients exhibiting early-onset myocardial infarction (as early as at 18 months and 3 years of age) support the notion that marked hypercholesterolemia contributes to the rapid progression of atherosclerotic plaque accumulation[9, 10].

In conclusion, we herein reported a case of marked transient hypercholesterolemia caused by the administration of low-dose mitotane as adjuvant chemotherapy for adrenocortical carcinoma. We recommend careful monitoring of the serum cholesterol level following the introduction of mitotane chemotherapy.

Acknowledgements

None.

Conflicts of Interest

None.

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