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Case Report

Acquired 11β-hydroxylase Deficiency by Inhaled Etomidate and its Analogues: A Mimic of Congenital Adrenal Hyperplasia

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Abstract

The increase in popularity of electronic cigarettes arouses great health concern. We describe a case of a 35-year-old female with chronic use of electronic cigarettes. She presented with secondary amenorrhea and prominent features of hyperandrogenism, including acne vulgaris, male-pattern alopecia, deepening of voice, and hirsutism. The initial biochemical workup revealed a profile indicating 11β-hydroxylase deficiency. However, genetic analysis did not show any evidence of *CYP11B1* mutation. This patient manifested the florid signs of disrupted steroidogenesis brought by chronic use of electronic cigarette oil containing etomidate and propoxate/isopropoxate, which are compounds structurally resembling etomidate. High clinical suspicion and sound understanding of the pharmacology and pathophysiology were instrumental in establishing the diagnosis for our present case.

Key Words: 11β-hydroxylase deficiency, etomidate, congenital adrenal hyperplasia, electronic cigarettes

Introduction

Among all congenital adrenal hyperplasia (CAH) cases, 0.2% to 8% are due to 11β-hydroxylase deficiency (1). The classical form of 11β-hydroxylase deficiency presents with virilization of prepubertal males and females, hypertension, and ambiguous genitalia in females (1). The nonclassical form presents with precocious adrenarche for both males and females (1). ACTH, 11-deoxycortisol (11-dF), 11- deoxycorticosterone (DOC), and androstenedione (ASD) are expected to be high whereas the levels of cortisol, corticosterone, and aldosterone would be low (1, 2). Despite low aldosterone and cortisol, patients develop hypertension because high levels of DOC and 11-dF may act as mineralocorticoid receptor agonists (1-3). Etomidate has been known to block adrenal 11β-hydroxylation, leading to increased levels of ACTH, 11-dF, 17-hydroxyprogesterone (17-OHP), and a decreased level of cortisol after short-term administration (4). With a recent concern over the misuse or abuse potential of etomidate (5), we identified a female chronic user of electronic cigarettes (e-cigarettes) (6), who inhaled the vapor produced from a liquid containing etomidate and its analogues propoxate/isopropoxate. After chronic use for 4 months, she developed a clinical and biochemical picture compatible with 11β-hydroxylase deficiency. Hence, chronic exposure to etomidate and its analogue propoxate/isopropoxate via e-cigarettes is considered the most likely cause of 11β-hydroxylase activity suppression in this case.

Case Presentation

A 35-year-old Chinese female patient from a nonconsanguineous family presented to our gynecologist in August 2023 for dysfunctional uterine bleeding, followed by secondary amenorrhea and features of virilization, including increase in facial hair requiring shaving every 3 days, acne vulgaris, male-pattern alopecia, and deepening of voice. She was gravida 4, para 1 + 3, and she had menarche at the age of 11 years.

Physical examination showed signs of hirsutism with increased hair growth around the lips, chin, chest wall, and lower abdomen, contributing to a raised modified Ferriman-Gallwey score of 7 (upper lip 3; chin 2; chest 1; upper abdomen 0; lower abdomen 1; upper and lower back 0; upper arm 0; thigh 0). Her body weight was 78.2 kg and height 165 cm. Cardiovascular, abdominal, and pelvic examinations were unremarkable, with normal genitalia and no clitoromegaly. Blood pressure was elevated to 165/101 mm Hg. Bedside transvaginal ultrasound revealed no polycystic ovaries nor adrenal mass. Non-classical CAH was suspected.

Upon further questioning, she also reported habitual use of e-cigarettes since June 2023, consuming half a capsule of e-cigarette oil per day (Fig. 1). She denied chronic drug use including azole-containing drugs, exogenous steroid, or any recreational drug use.

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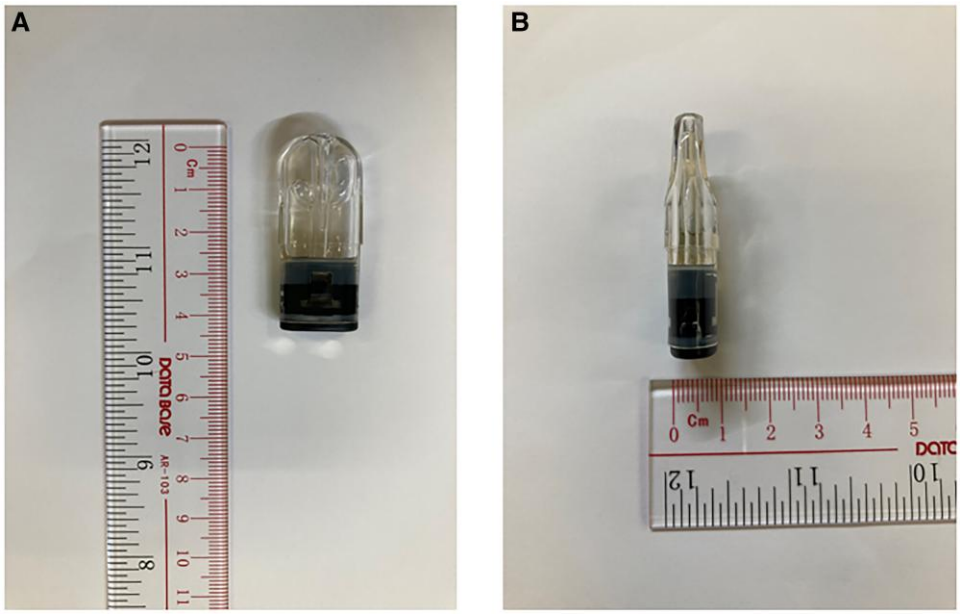

Figure 1. Capsule of the etomidate and its analogues propoxate/isopropoxate containing e-cigarette oil (A, view from front; B, view from side).

Diagnostic Assessment

Upon presentation, her initial serum hormonal profile showed raised total testosterone, ASD, dehydroepiandrosterone sulphate, and 17-OHP (Table 1). LH and FSH were slightly suppressed for follicular phase, and estradiol was normal (Table 1).

ACTH stimulation test incorporating cortisol and other CAH markers was arranged. Results showed a blunted cortisol response, grossly elevated 11-dF, and no significant rise in 17-OHP (Table 2). Baseline plasma ACTH level was raised (Table 1). As for mineralocorticoid axis, aldosterone level was low and plasma renin activity was low normal (Table 1). Her renal function profile including sodium and potassium levels were unremarkable all along. TSH and prolactin levels were normal. Her biochemical results were summarized in Table 1.

A 24-hour urine sample for steroid profile demonstrated markedly increased androgen metabolites, including metabolites of dehydroepiandrosterone (7). Tetrahydro-11-deoxycortisol, a metabolite of 11-dF, and tetrahydro-deoxycorticosterone, a metabolite of DOC, were also markedly elevated (7) (Fig. 2). The overall urine steroid profile picture was compatible with 11β-hydroxylase deficiency. Computed tomography of the abdomen showed significant diffuse thickening of bilateral adrenal glands, suggestive of adrenal hyperplasia without ovarian or adnexal mass (Fig. 3).

Genetic workup for 11β-hydroxylase deficiency by analysis of *CYP11B1* gene was pursued, using PCR and Sanger sequencing to cover all coding exons and the flanking regions (15 bp), revealing no pathogenic variant. Multiplex ligation-dependent probe amplification analysis with probemix P495-A1 CYP11A1-CYP11B1-CYP11B2 (MRC-Holland, Amsterdam, the Netherlands) showed no exon deletion.

In view of history of e-cigarette use, broad-spectrum toxicology analysis was performed on urine and e-cigarette oil specimens. Urine specimen was analyzed with liquid chromatography with quadrupole time-of-flight mass spectrometry (SCIEX X500R QTOF, Framingham, MA, USA), whereas e-cigarette oil specimen was analyzed with liquid chromatography with quadrupole time-of-flight mass spectrometry and high-performance liquid chromatography-diode array detector (Waters Xevo G2-XS Qtof, Milford, MA, USA; and Agilent HPLC-DAD 1260 Infinity series, Santa Clara, CA, USA). In the urine sample, etomidate metabolite (etomidate acid), propoxate/isopropoxate, amphetamine, and methamphetamine with its metabolite pholedrine were detected. In the e-cigarette oil sample, propoxate/isopropoxate and etomidate were detected. Propoxate and isopropoxate are propyl and isopropyl esters of etomidate acid, respectively (8-11). Because propoxate and isopropoxate share similar physical and chemical properties, they were not differentiated in the aforementioned assay.

Treatment

The patient was started on oral hydrocortisone replacement with a total dose of 15 mg per day with stress dose instruction from March 2024. She was also started on amlodipine 2.5 mg daily since April 2024 for blood pressure control. Smoking cessation was advised.

Outcome and Follow-up

In the follow-up visit in March 2024, the patient was concerned about increase in skin pigmentation, which might be related to a high ACTH level. At her visit in April 2024, amenorrhea and deepening of voice persisted. Her latest office blood pressure was 153/98 mm Hg. She continued e-cigarette use despite being advised to quit. However, she has avoided follow up at the endocrine clinic after April 2024.

Discussion

Etomidate is a drug commonly used for sedation, induction of general anesthesia, and during intubation in emergency departments and intensive care units (12). Common side effects include postoperative nausea and vomiting, and pain on

Table 1. A summary of blood investigation results

	Test	Value	Reference interval
Pituitary hormone	ACTH	47.5 pmol/L (215.9 pg/mL)	1.6-13.9 pmol/L (7.3-63.2 pg/mL)
	Prolactin	477 mIU/L (22.7 ng/mL)	102-496 mIU/L (4.9-23.6 ng/mL)
	LH	1.3 IU/L (1.3 mIU/mL)	2.4-12.6 IU/L (2.4-12.6 mIU/mL)
	FSH	2.0 IU/L (2.0 mIU/mL)	3.5-12.5 IU/L (3.5-12.5 mIU/L)
Ovarian hormone	Estradiol	236 pmol/L (64.0 pg/mL)	<854 pmol/L (<231 pg/mL)
Androgen axis	Testosterone	16.1 nmol/L (464.0 ng/dL)	<1.7 nmol/L (<49.0 ng/dL)
	Androstenedione	97.0 nmol/L (2779.4 ng/dL)	1.1-6.5 nmol/L (31.5-186.2 ng/dL)
	17-OHP	13 nmol/L (433 ng/dL)	< 4 nmol/L (<133 ng/dL)
	DHEAS	15.0 µmol/L (555.6 µg/dL)	1.7-9.2 µmol/L (63.0-340.8 µg/dL)
11β-hydroxylase substrate	11-dF	351 nmol/L (12 145 ng/dL)	<4.3 nmol/L (<149 ng/dL)
Mineralocorticoid axis	Aldosterone	<50 pmol/L (<2 ng/dL)	≤ 488 pmol/L (≤ 18 ng/dL)
	Plasma Renin Activity	0.25 ng/mL/hour (0.25 µg/L/hour)	0.24-5.5 ng/mL/hour (0.24-5.5 µg/L/hour)
	Sodium	140 mmol/L (140 mEq/L)	136-145 mmol/L (136-145 mEq/L)
	Potassium	3.5 mmol/L (3.5 mEq/L)	3.4-5.0 mmol/L (3.4-5.0 mEq/L)
Renal function	Urea	4.7 mmol/L (13.2 mg/dL)	3.0-7.4 mmol/L (8.4-20.7 mg/dL)
	Creatinine	65 µmol/L (0.74 mg/dL)	47-82 µmol/L (0.53-0.93 mg/dL)
Thyroid function	TSH	0.56 mIU/L (0.56 µIU/mL)	0.35-4.94 mIU/L (0.35-4.94 µIU/mL)

Abbreviations: DHEAS, dehydroepiandrosterone sulphate; 11-dF, 11-deoxycortisol; 17-OHP, 17-hydroxyprogesterone.

Table 2. ACTH stimulation test result (250 mg tetracosactin injected at 0 minutes)

Test	0 minutes	30 minutes	60 minutes
17-OHP	11 nmol/L (367 ng/dL)	16 nmol/L (533 ng/dL)	18 nmol/L (600 ng/dL)
Cortisol	138 nmol/L (5.0 µg/dL)	160 nmol/L (5.8 µg/dL)	195 nmol/L (7.1 µg/dL)
21-dF	<2.5 nmol/L (<86.6 ng/dL)	<2.5 nmol/L (<86.6 ng/dL)	<2.5 nmol/L (<86.6 ng/dL)
11-dF	351 nmol/L (12 145 ng/dL)	408 nmol/L (14 118 ng/dL)	423 nmol/L (14 637 ng/dL)

Abbreviations: 11-dF, 11-deoxycortisol; 17-OHP, 17-hydroxyprogesterone; 21-dF, 21-deoxycortisol.

injection (12, 13). A reported case of a patient on long-term etomidate infusion demonstrated a direct reversible adrenocortical suppression effect of the drug, showing a low basal serum cortisol level and blunted response to ACTH stimulation upon etomidate infusion (14). Within 24 hours of stopping the infusion, the patient demonstrated a rise in cortisol level, a drop in ACTH level, and a response to ACTH stimulation (14). Another study on patients receiving an elective surgery showed that etomidate infusion could suppress adrenocortical response to ACTH for 24 hours (15). However, there is no report on etomidate's adrenocortical suppression effect via inhalation.

Because of its rapid onset and easy titration, etomidate was proposed to be an acute treatment option for severe Cushing syndrome for its action on 11β-hydroxylase (16). Some institutions have developed a protocol on etomidate infusion for rapid control of hypercortisolism (17). Such use should require close monitoring in an intensive care setting.

E-cigarette oil contains propoxate/isopropoxate. As mentioned, propoxate and isopropoxate are the propyl ester and isopropyl ester of etomidate acid, respectively, whereas etomidate is an ethyl ester (8-11) (Fig. 4). Propoxate is an anesthetic for cold-blooded vertebrates, but has never been used on humans (18, 19). Isopropoxate has not been reported to be of any clinical use. The lack of their clinical application on humans might explain the lack of studies on it.

The 11β-hydroxylase is an enzyme catalyzing the conversion of 11-dF to cortisol, DOC to corticosterone, and ASD to 11β-hydroxyandrostenedione in the adrenal cortex (7, 20, 21). Common presentations of congenital deficiency of 11β-hydroxylase include genital ambiguity in females and salt retention in the neonatal period, whereas presentation in later stages of life include hyperandrogenism and hypertension (7). Acquired cause of enzyme inhibition would include usage of

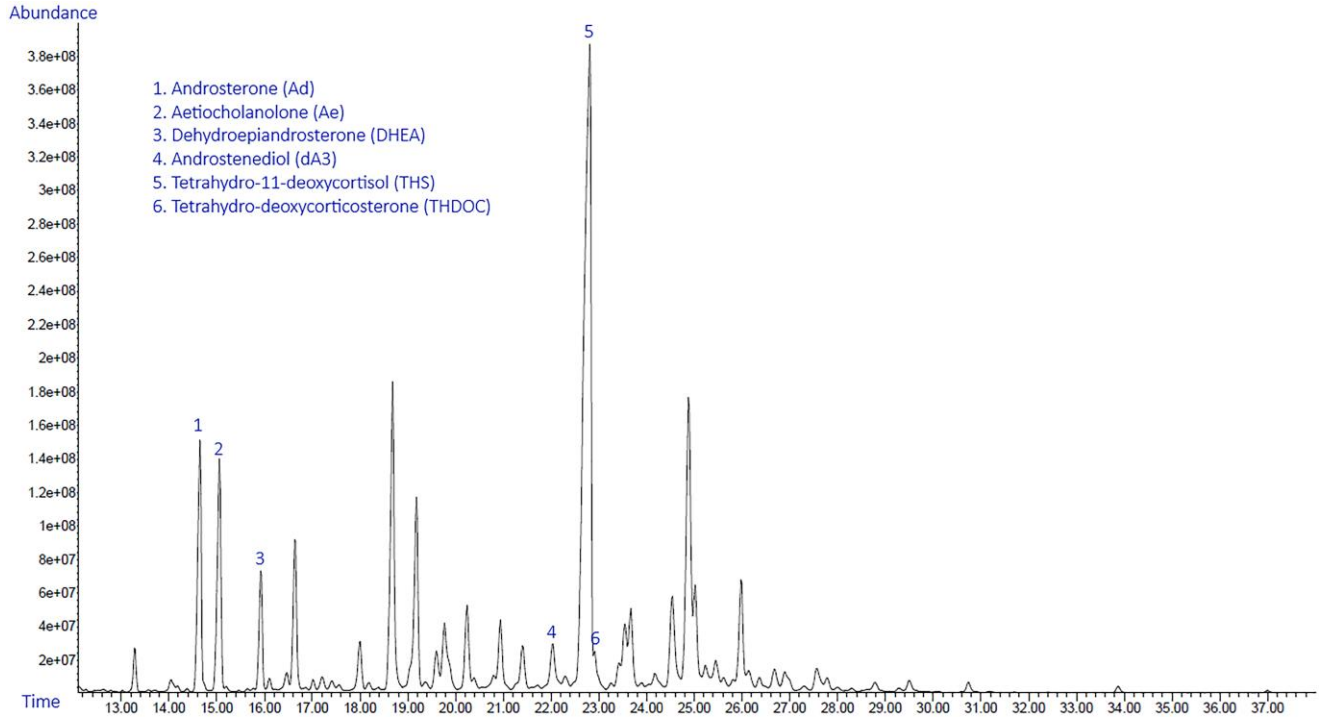

Figure 2. Chromatogram of patient's urine steroid profile, with significantly elevated peaks highlighted in the diagram.

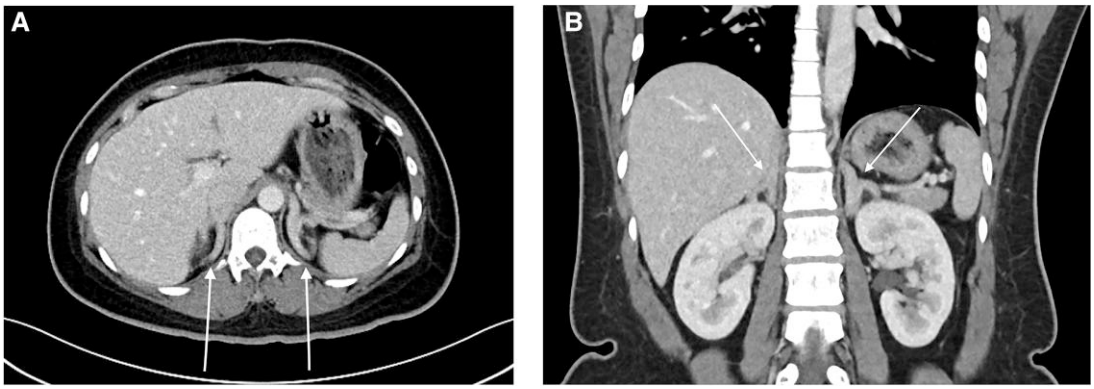

Figure 3. Computed tomography scans of the patient. Post-contrast computed tomography scan of abdomen with both axial (A) and coronal (B) views showed diffuse uniform thickening of bilateral adrenal glands, compatible with adrenal hyperplasia.

metyrapone and azole drugs, such as ketoconazole for mucosal candidiasis and cutaneous fungal infections (7, 22).

In this patient with clinical features of androgen excess and biochemical features of 11β-hydroxylase suppression, genetic tests were performed as part of diagnostic process. With negative genetic tests, thorough investigation on potential acquired causes giving rise to similar presentation was mandated. Upon reviewing the drug history of this patient, the use of e-cigarettes preceded the onset of hyperandrogenism symptoms by 4 months. Because analysis of the e-cigarette oil revealed etomidate and propoxate, which could have adrenocortical suppression effects (14), its chronic use appeared to be the main culprit for her inhibited 11β-hydroxylase activity. The negative results on Sanger sequencing and multiplex ligation-dependent probe amplification analysis supported our hypothesis because no other gene is known to cause congenital 11β-hydroxylase deficiency (23).

Clinical assessment and evaluation of biochemical tests are crucial in establishing the diagnosis and subsequent monitoring of the patient. Detailed clinical history, including any menstrual cycle disturbance and history of e-cigarette or other recreational drug use, should be taken. Blood pressure should be monitored and features of hyperandrogenism and glucocorticoid insufficiency should be specifically looked for during physical examination. Exposure and abstinence could be confirmed by urine toxicology testing. Nonbiological samples, such as e-cigarette liquid, could be sent for toxicology analysis to confirm the source of etomidate and its analogues propoxate/isopropoxate. Biochemically, plasma levels of sodium and potassium should be monitored for mineralocorticoid effect. Serum levels of androgens including ASD, testosterone and dehydroepiandrosterone sulphate, and/or 17-OHP could be markers for disease severity. The effect of hyperandrogenism should be less evident in male, thus a heightened suspicion

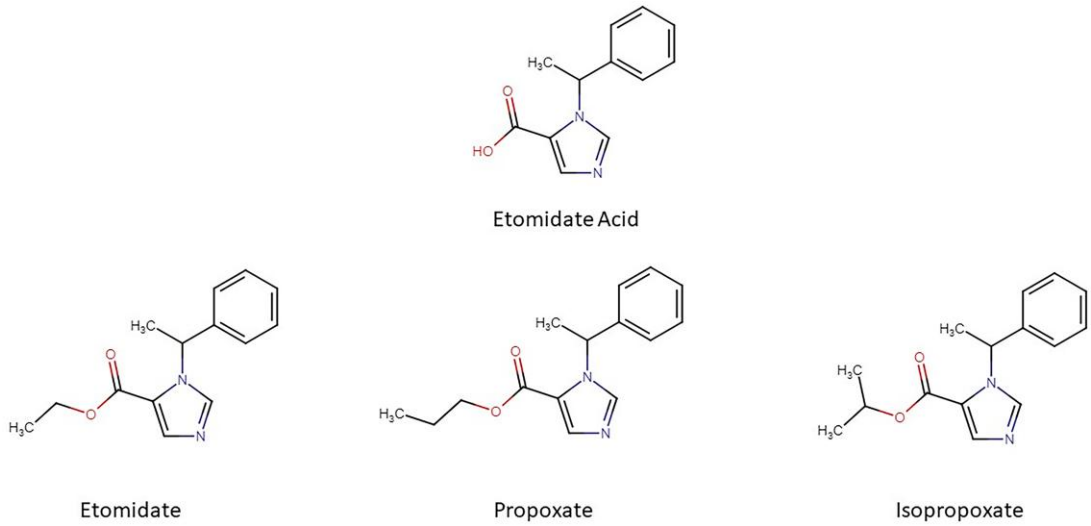

Figure 4. Chemical structure of etomidate acid (8), etomidate (9), propoxate (10), and isopropoxate (11).

based on other clinical and biochemical features should be warranted.

The patient started using e-cigarettes as a substitute for traditional cigarettes. She found the e-cigarette oil relaxing, with pleasant fruity smell. The heightened awareness on the detrimental effect of traditional cigarettes, and widespread antismoking campaign might encourage some smokers to search for a novel substitute, contributing to the popularity of e-cigarettes. It is also reported that etomidate brings a sedative, hypnotic, and relaxing effect, which might be the pleasure pursued by its users (24).

There are a few limitations to our case study. The resolution of clinical and biochemical manifestations after her abstinence has yet to be demonstrated. There is a paucity of studies demonstrating propoxate's effect on human. It would be ideal to have evidence from more clinical cases and/or larger scale study. Our toxicology analysis was qualitative rather than quantitative, even though the exact "dosage" could never be easily quantified with inhalation use of etomidate and its analogues propoxate/isopropoxate. Our routine method of urine toxicology analysis was also unable to differentiate between propoxate and isopropoxate. Our genetic analysis, albeit comprehensive for *CYP11B1* mutation, could not cover promoter region or remote intronic mutations.

To the best of our knowledge, this is the first case reported to manifest adrenocortical suppression following chronic abuse of etomidate and its analogues propoxate/isopropoxate via e-cigarette use. Physician awareness is important in identifying cases of chronic etomidate and its analogues propoxate/isopropoxate use, especially when encountering patients with clinical presentation of apparent 11β-hydroxylase deficiency.

Learning Points

- Etomidate and its analogues propoxate/isopropoxate could be emerging drugs of abuse in e-cigarette users
- Chronic use of etomidate and its analogues propoxate/isopropoxate via e-cigarette could exert strong adrenocortical suppression effect
- Acquired cause should be considered for cases with apparent 11β-hydroxylase deficiency, especially for patients with a positive reproductive history

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Contributors

All authors made individual contributions to authorship. C.Y.L., T.M.A.H., Y.T.T.C., and P.L.S.C. were involved in drafting the manuscript. Y.T.T.C. and Y.K.C. were involved in toxicology analysis. C.M.J.C. was involved in clinical assessment and management of the patient. Y.K.C. and P.L.S.C. were involved in providing overall supervision and approval of the work. All authors reviewed and approved the final manuscript.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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