



# Acute mesenteric ischemia and hepatic infarction after treatment of ectopic Cushing's syndrome

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## Summary

Patients with Cushing's syndrome and excess exogenous glucocorticoids have an increased risk for venous thromboembolism, as well as arterial thrombi. The patients are at high risk of thromboembolic events, especially during active disease and even in cases of remission and after surgery in Cushing's syndrome and withdrawal state in glucocorticoid users. We present a case of Cushing's syndrome caused by adrenocorticotrophic hormone-secreting lung carcinoid tumor. Our patient developed acute mesenteric ischemia after video-assisted thoracoscopic surgery despite administration of sufficient glucocorticoid and thromboprophylaxis in the perioperative period. In addition, our patient developed hepatic infarction after surgical resection of the intestine. Then, the patient was supported by total parenteral nutrition. Our case report highlights the risk of microthrombi, which occurred in our patient after treatment of ectopic Cushing's syndrome. Guidelines on thromboprophylaxis and/or antiplatelet therapy for Cushing's syndrome are acutely needed.

## Learning points:

- The present case showed acute mesenteric thromboembolism and hepatic infarction after treatment of ectopic Cushing's syndrome.
- Patients with Cushing's syndrome are at increased risk for thromboembolic events and increased morbidity and mortality.
- An increase in thromboembolic risk has been observed during active disease, even in cases of remission and postoperatively in Cushing's syndrome.
- Thromboprophylaxis and antiplatelet therapy should be considered in treatment of glucocorticoid excess or glucocorticoid withdrawal.

## Background

Cushing's syndrome (CS) results from chronic exposure to excess cortisol production and secretion from the adrenal cortex. Hypertension, glucose intolerance, dyslipidemia and osteoporosis are common complications in CS. Complications of CS may greatly affect the quality of

life and mortality. Patients with CS have an increased risk for venous thromboembolism, myocardial infarction and stroke (1). In addition, excess exogenous glucocorticoids increase venous thromboembolism (VTE) risk (2). However, specific guidelines for the prevention



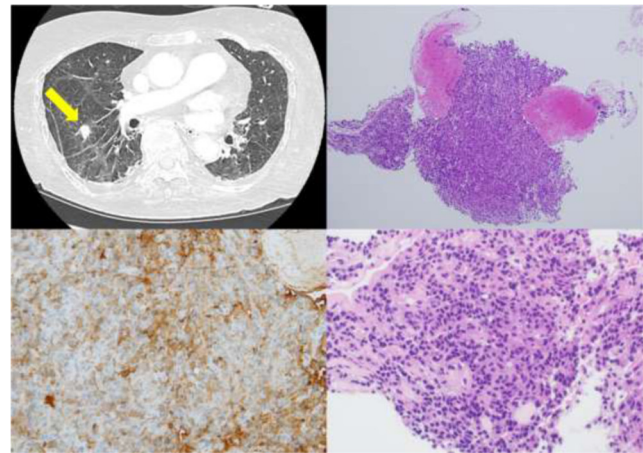
of thrombosis in such patients have not been described. Our patient developed acute mesenteric ischemia and hepatic infarction, which occurred after treatment and glucocorticoid withdrawal period of ectopic CS. This case has a merit of clinical attention.

## Case presentation

A 65-year-old Japanese woman was referred for further evaluation of Cushing's syndrome (CS). Her case history included the following: 20 years of paroxysmal arterial fibrillation under treatment with warfarin potassium; 10 years of hypertension and diabetes with drug resistance and 5 years of proximal muscle weakness. She presented with a moon face, central obesity, skin atrophy and plethora. Blood pressure was 128/78 mmHg and was treated with antihypertensive agents (40 mg telmisartan, 5 mg amlodipine, 5 mg bisoprolol, 40 mg furosemide and 25 mg spironolactone). The HbA1c level was 9.3%, even under treatment with oral hypoglycemic agents (1 mg glimepiride, 15 mg pioglitazone and 100 mg vildagliptin).

Basal ACTH and cortisol levels in plasma were up to 205 pg/mL and 79 µg/dL, respectively. Urinary free cortisol (UFC):creatinine ratio was up to 2035 µg/g. Salivary free cortisol was not measured. The patient was diagnosed with ectopic ACTH syndrome after endocrinological analyses. She was administered steroidogenesis inhibitors, metyrapone and mitotane, to suppress cortisol secretion. Serum cortisol and UFC levels fell to around 20 µg/dL and 200 µg/g of creatinine, respectively. We were unable to identify the source of ACTH secretion for 7 months. Finally, repeated computed tomography (CT) scans and FDG-PET/CT showed a nodule of 10 mm diameter in segment four of the right lung (Fig. 1). Trans-bronchial lung biopsy was performed, and the patient was histologically diagnosed with a typical carcinoid with immunoreactive ACTH (Fig. 1).

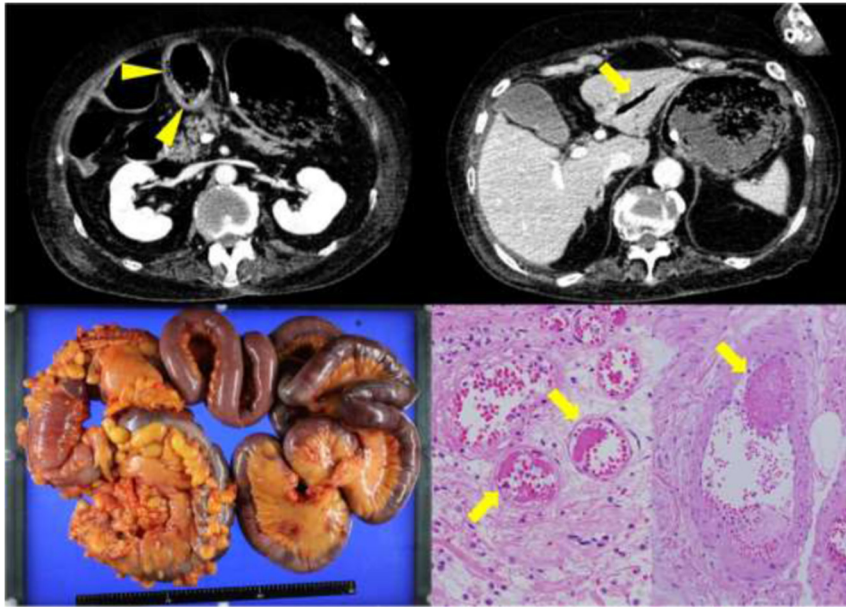
Video-assisted thoracoscopic surgery was performed, and the right middle lobe of the lung was resected. Complete anatomical resection with a negative resection margin was confirmed. The level of plasma ACTH (minimum detection limit 1 pg/mL) fell to 3 pg/mL immediately after the operation, and glucocorticoid replacement therapy was subsequently administered. Therefore, disease cure was evaluated. She was administered 200 mg of hydrocortisone intravenously on the day of the operation and on postoperative day (POD) 1, 100 mg at POD 2 and 50 mg at PODs 3 and 4.



**Figure 1**  
CT scans show a 10-mm-diameter nodule in segment four of the right lung (left upper panel). Formalin-fixed and paraffin-embedded sample from the lung tumor shows cells with an eosinophilic cytoplasm, low nuclear grade and oval nuclei. The cells show rosette structures (right panel). The tumor was histologically diagnosed as a typical carcinoid with immunoreactive ACTH (left lower panel).

## Investigation

The patient's clinical features improved during the follow-up. However, she presented with a body temperature up to 38.5°C on POD 4. Blood tests showed a white blood cell count of 13 350/mL, C-reactive protein level of 6.7 mg/L and blood sugar level of 250 mg/dL. Blood culture did not detect any bacteria. CT scans showed a thrombus at the merging section of the left jugular and subclavian veins and revealed no notable origin of infection. She was administered 10 000 IU of heparin sodium by continuous intravenous infusion in the perioperative period. Warfarin potassium was added to a heparin infusion since POD 27. Echocardiography showed normal chamber sizes, normal function of heart valves, absence of a thrombus or vegetation and normal ventricular systolic function on POD 29. A total of 50 mg of hydrocortisone was administered enterally from PODs 5 to 8, and then it was reduced to 30 mg since POD 9. The dosage of hydrocortisone was further reduced from 30 mg to 15 mg on POD 29. Thirty days after the operation, the patient went into sudden shock. Blood pressure and heart rate were 64/43 mmHg and 120 bpm, respectively. An electrocardiogram showed sinus tachycardia. She had abdominal pain, distention and guarding. Blood tests indicated a white blood cell count of 34 140/mL, C-reactive protein level of 40.2 mg/L, arterial blood pH of 7.50, bicarbonate level of 29.3 mmol/L, base deficit of 0.9 mmol/L, international normalized ratio of prothrombin time of 1.2 and activated partial



**Figure 2**

Contrast-enhanced transverse CT scan shows intestinal dilatation with collection of gas, gas in the bowel wall (left upper panel, arrowheads) and hepatic portal venous gas (right upper panel, arrow). Continual necrosis was found between the ileum and transverse colon (left lower panel). Formalin-fixed and paraffin-embedded sample shows capillary microthrombi of the mucous membrane (right lower panel, arrow).

thromboplastin time of 45.6s (range, 26–36). Enhanced CT findings showed intestinal dilatation and hepatic portal venous gas (Fig. 2). Occlusion of either the superior mesenteric or celiac arteries could not be found.

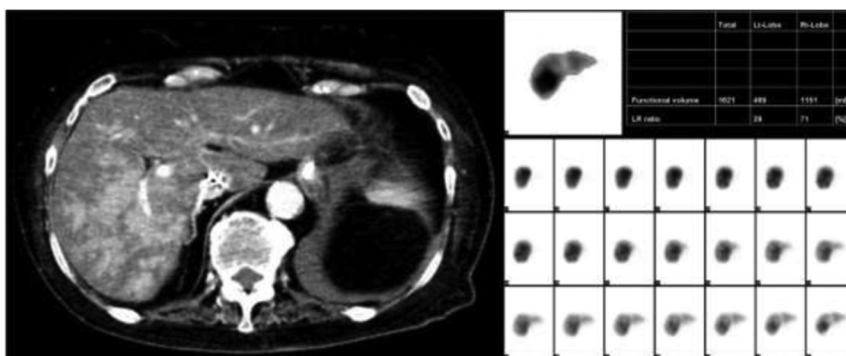
### Treatment

An emergency laparotomy was performed, which showed continual necrosis between the ileum and transverse colon (Fig. 2). A total length of 3m of intestine was resected and ileostomy was performed. Hemorrhagic infarction due to multiple microthrombi in the capillaries was histologically identified (Fig. 2).

### Outcome and follow-up

The patient was administered 15 000 IU of heparin sodium by continuous intravenous infusion in the perioperative period followed by warfarin potassium. Heparin was discontinued when the international

normalized ratio of prothrombin time was prolonged into the therapeutic range (around 2.0). Surgical resection of the intestine was associated with the impairment of absorption and digestion of nutrients. She was supported by total parenteral nutrition. After the operation, laboratory tests showed a continuous increase in serum transaminase levels. CT scans demonstrated the presence of peripheral hepatic infarction, with irregular contours and extending over the entire liver segments (Fig. 3). Uptake of Tc-99m-labeled galactosyl human serum albumin in the liver, which evaluates hepatic function, was reduced at the lesions (Fig. 3). The indocyanine green clearance test showed 22% retention at 15 min. She continued to receive warfarin potassium for the treatment of hepatic infarction. She was transferred to another hospital for long-term hospitalization. She developed repeated bouts of pneumonia and was treated with antibiotics. She died 2 years and 3 months later in a state of renal failure.



**Figure 3**

CT scan shows irregularly shaped infarctions extending over the entire liver segment (left panel). The uptake of Tc-99m-labeled galactosyl human serum albumin in the liver was reduced at the infarctions (right panel).



## Discussion

The etiology of mesenteric ischemia represents a complex of diseases, including acute arterial mesenteric ischemia, acute venous mesenteric ischemia, non-occlusive mesenteric ischemia and ischemia/reperfusion injury. The risk for acute mesenteric thromboembolic events has a variety of causes, including mesenteric arterial/venous occlusion, inflammation, low flow and vasospasm (3). However, hepatic infarctions are thought to be extremely rare because many accessory and collateral vessels create a complex compensatory system that prevents ischemia or infarction. Hepatic infarction may result from shock, sepsis, anesthesia, biliary disease and diabetic ketoacidosis or surgical factors (4). The occurrence of multiple peripheral and extending infarctions in our case might have been due to a mixed origin of arterial thromboembolism and reduced portal flow from intestinal resection.

Increased coagulability has been observed in patients treated with glucocorticoids and in patients with CS (5). Patients with CS who are treated with glucocorticoids have an increased risk for thromboembolism, especially venous thromboembolism, myocardial infarction and stroke (2, 6). Mortality is increased in patients with CS, with the highest risk observed in patients with persistent disease. In fact, cortisol excess is known to stimulate the synthesis of fibrinogen and von Willebrand factor, which facilitate platelet aggregation. Additionally, glucocorticoids upregulate the synthesis of plasminogen activator inhibitor type 1. In a previous study, survival analysis showed a significantly higher morbidity and mortality due to thromboembolic events in the group without anticoagulants than that in the group treated with anticoagulants in the perioperative period in patients with CS (5). Therefore, use of low-dose heparin has been suggested in the perioperative period (7, 8). However, specific guidelines for the prevention of thrombosis with CS have not been described (8). Furthermore, an increase in cardiovascular risk has been observed, even in the cases of remission of CS (9). The risk for postoperative events increases in patients with Cushing's disease (10). The source of excess ACTH and malignancy was considered to be totally resected in our patient. However, malignancy itself may induce a thromboembolic state and affect mortality in patients with CS who suffer from an ectopic ACTH source.

In conclusion, this case report emphasizes that patients with excess glucocorticoids or glucocorticoid withdrawal have a high risk for thromboembolism. In

addition to thromboprophylaxis, cautious lowering of glucocorticoids and antiplatelet therapy should be considered in treatment of such patients, when additional risk factors for thromboembolism, such as diabetes, immobility and surgery, are encountered.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Patient consent

The patient died. Consent was obtained from the husband for publication of this case report.

### Author contribution statement

S T, S M, S Y, K K, T N, Y W, K T and M D contributed equally to the diagnosis and management of the patient. D K and T T performed video-assisted thoracoscopic surgery. Y S and K H performed intestinal resection and ileostomy. S T wrote the report. All authors read and approved the final manuscript. Written consent to publish was obtained.

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