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Acute adrenal insufficiency secondary to bilateral adrenal haemorrhage

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Acute adrenal insufficiency is a clinical syndrome caused by a sudden and significant cortisol deficiency, which is life-threatening. Quite frequently, the diagnosis of this disease entity in subjects with normal secretory function is a challenge for clinicians. We present a female patient with bilateral adrenal haemorrhage secondary to type 2 heparin-induced thrombocytopaenia.

This 71-year-old patient after the procedure of right knee arthroplasty conducted 8 days before, with ongoing anticoagulant prophylaxis with enoxaparin (40 mg/d), was admitted to the emergency department (ED) due to abdominal pain (score 9/10). Her medical history revealed treatment due to hypertension and type 2 diabetes. Physical and laboratory tests showed no clinically significant abnormalities. A chest X-ray showed a dilated aortic arch with atherosclerotic lesions, and an abdominal ultrasound revealed hepatic steatosis and atherosclerosis of abdominal aorta. After symptomatic treatment, the patient was discharged home. On the next day, the patient was readmitted to the ED due to deterioration of contact and recurrence of abdominal pain. Laboratory tests showed a gradual increase in leucocytosis and concentration of C-reactive protein (CRP), the presence of thrombocytopaenia and acute severe hyponatraemia, and a relatively mild hyperglycaemia (Tab. 1). The patient had a CT scan of the aorta with contrast, which showed no pathology of the aorta or its branches, except for atherosclerosis, but which showed bilateral enlargement of the adrenal glands, up to 3 cm, surrounded by densities — status post haemorrhage (Fig. 1A). Hormonal diagnostics showed a very low level of blood cortisol and dehydroepiandrosterone sulphate with a high level of adrenocorticotropic hormone (ACTH)

Table 1. *Selected results of laboratory tests performed during the 1st and 2nd stay at the emergency department (ED)*

Laboratory tests	1st stay 10/11/2021	2nd stay 11/11/2021
WBC [×10⁹/L]	11.2	13.8
HGB [g/dL]	11.7	12.9
PLT [×10⁹/L]	192	76
CRP [mg/L]	49.2	110.7
Na [mmol/L]	133	122
K [mmol/L]	4.3	3.8
Creatinine [μmol/L]	58.2	70.8
Glucose [mmol/L]	10.55	5.63
INR	1.27	1.24
APTT [s]	29.4	28.6

WBC — white blood cells; HGB — haemoglobin; PLT — platelets; CRP — C-reactive protein; Na — sodium; K — potassium; INR — International Normalized Ratio; APTT — activated partial thromboplastin time

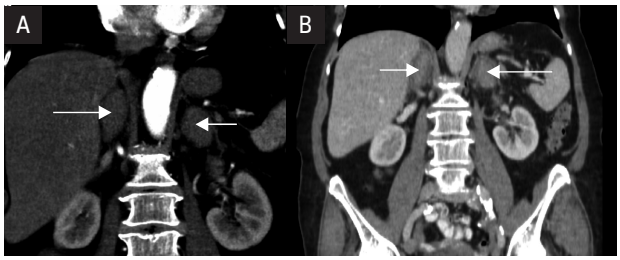

Figure 1. *A CT scan of the aorta with contrast (***A***); a control CT of the abdominal cavity with contrast (***B***)*

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Table 2. *Selected results of laboratory tests performed during previous hospitalisations at the Department of Endocrinology and Metabolic Diseases*

Laboratory tests	Hospitalisation			
	1st 12–22/11/2021	2nd 27–30/12/2021	3rd 23–26/05/2021	4th 08–11/08/2021
Serum cortisol 6:00/22:00	1.3/< 1.0	< 1.0/< 1.0	< 1.0/< 1.0	4.7/2.9
ACTH 6:00/22:00	530.9/244.2	80.52/6.38	127.4/13.36	299.6/95.19
DHEAS	< 4.8	< 4.8	< 4.8	< 4.8
PRA	7.95	0.43	0.31	1.63
Na	137–138	141	142	138
K	3.8–4.3	3.6	4.0	4.5
Glucose	4.95	5.47	5.56	5.32

ACTH — adrenocorticotropic hormone; DHEAS — dehydroepiandrosterone sulphate; PRA — plasma renin activity; Na — sodium; K — potassium

and an increased plasma renin activity. Antibodies against heparin-PF4 complex were present, which was confirmation of immune aetiology of heparin-induced thrombocytopaenia. A control CT of the abdominal cavity with contrast revealed further evolution of haemorrhagic lesions in the adrenals (Fig. 1B). The treatment included hydrocortisone, parenteral hydration, empiric antibiotic therapy with ceftriaxone, and thromboprophylaxis with fondaparinux, which resulted in general improvement of the patient's condition and normalization of the number of platelets and leukocytes, reduction in the CRP level, and control of natraemia. Due to a stable level of electrolytes and normal blood pressure, fludrocortisone was not introduced. The patient was re-hospitalised 3 times during the year for the purpose of clinical evaluation. During the last hospitalisation, the patient felt well. She receives replacement therapy with hydrocortisone products 20 mg/d, and no complications of glucocorticosteroid therapy are observed. During the last hospitalisation a short ACTH stimulation test for cortisol was performed, which produced no response. Summary results of laboratory tests are presented in Table 2. Last follow-up CT showed smaller adrenal glands than before and further evolution of posthaemorrhagic changes. The patient was diagnosed with primary adrenal insufficiency resulting from the past bilateral adrenal haemorrhage secondary to autoimmune heparin-induced thrombocytopaenia.

Bilateral adrenal haemorrhage is a rarely diagnosed cause of acute adrenal insufficiency, and a correct diagnosis, in the shortest time possible, may save the patient's life [1]. Difficulties in establishing the diagnosis may be related to both clinical symptoms of low specificity, including abdominal pain, fever, and hypotension, as well as to laboratory abnormalities, including hyponatraemia, hyperkalaemia, leucocytosis, and reduced haemoglobin level [1]. Patients with a high risk of bilateral adrenal haemorrhage are those treated with heparin (regardless of the heparin type and route of administration) for more than 3 days, with thrombocytopaenia (not necessarily heparin-induced), with sepsis, or after an invasive radiological procedure [2].

Bilateral adrenal haemorrhage may also develop as a result of type 2 heparin-induced thrombocytopaenia (HIT2), due to thrombosis of a central adrenal vein, which leads to a later haemorrhagic infarction of adrenals [3]. To estimate the clinical probability of HIT, a predictive clinical principle, 4T, is applied [4]. In the reported patient, due to a high clinical probability of HIT (> 50% fall in platelet count — 2 points; within 5–10 days of exposure to heparin — 2 points; bilateral adrenal haemorrhage could be potentially associated with thrombosis of central adrenal vein — 1 point; there was no other evident explanation for the fall in the platelet count — 2 points), antibodies against the heparin–platelet factor 4 (PF4) complex were measured, which confirmed the diagnosis of HIT.

When bilateral adrenal haemorrhage is clinically suspected, computed tomography is the gold standard for diagnosis [5]. In the described patient, haemorrhage was diagnosed accidentally during a contrast-enhanced aortic CT scan performed due to suspicion of aortic dissection.

The presented clinical situation indicates difficulties in the diagnosis of acute adrenal insufficiency secondary to bilateral adrenal haemorrhage. Therefore, it should be remembered that it is important to exclude adrenal haemorrhage in patients treated with heparin, who reveal abdominal pain with fever, hypotension, and electrolyte abnormalities typical of adrenal insufficiency.

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