CASE REPORT

JIACM 2023; 24 (1): 58-63

ITP Associated Bilateral Adrenal Haemorrhage: Near Kill and Saved

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Abstract

Bilateral adrenal haemorrhage (BAH) is a rare but potentially fatal entity that carries a high mortality rate. Most cases are associated with sepsis, antiphospholipid syndrome, use of anticoagulants, trauma or surgery. In this case report, we present a case of BAH, in a previously healthy man, with a recent history of corticosteroid use for his immune thrombocytopenic purpura (ITP). Our case emphasizes the ambiguous clinical presentation of BAH, that poses a great challenge in the establishment of a early and correct diagnosis. We further explain the pathophysiology, diagnostic clues and therapeutic approach to this rare entity. ITP is an immune-mediated, acquired disease reported in adults as well as children. It is characterised by transient or persistent decreases in platelet count. We present a rare case repot of bilateral adrenal haemorrhage caused by ITP, saved from an adrenal crisis by steroid therapy ongoing for his ITP. Despite the high mortality associated with adrenal haemorrhage, our patient survived and is doing well on follow-up.

Key words: ITP, bleeding crisis, adrenal haemorrhage, adrenal crisis.

Introduction

Bilateral adrenal haemorrhage (BAH) is a life-threatening condition which usually leads to an adrenal crisis and death, if not diagnosed and treated in time[1]. The pathogenesis of this rare entity is thought to be related to the increased vascularisation of adrenal glands in a physiological response to stressful events[2,3]. This vascular congestion causes haemorrhage in the adrenals, usually unilaterally but rarely bilaterally. Post-operative status, thromboembolic disease, and coagulopathy are reported causes of such a response, among many other causes[3]. Identifying the signs and symptoms of an oncoming adrenal crisis is of utmost importance, as it is overshadowed by signs of the underlying cause[2]. Serum cortisol, 24-hour urinary cortisol, dexamethasone suppression test and adrenocorticotropic hormone (ACTH) test, are helpful in confirming diagnosis of adrenal crisis, further supported by computed tomography (CT), which confirms adrenal haemorrhage. CT is pivotal for the early diagnosis of adrenal haemorrhage and commencing corticosteroid replacement therapy to prevent mortality[4].

ITP is as a haematologic disorder which is characterised by isolated thrombocytopenia without any apparent cause. The risk of spontaneous haemorrhage due to low platelet count is important in determining the prognosis of ITP. Patients have an estimated risk of fatal haemorrhage of approximately 5% throughout their lifetime; however, this risk of major haemorrhagic complications exponentially increases with age[5].

The clinical characteristics of ITP are mucocutaneous lesions such as petechiae or ecchymosis, epistaxis, easy bruising, and gingival bleeding[6].

Our patient reported a rare presentation of ITP, causing spontaneous bilateral adrenal haemorrhage, leading to Addison's crisis, which was pre-emptively treated by the ongoing treatment with corticosteroids, for ITP itself.

Case history

A 48-year-old male patient, with no significant medical history, presented to our hospital in September 2021 with complaints of recurrent loose stools (10 - 12 episodes), nausea, 2 - 3 episodes of vomiting, generalised pain in the abdomen, generalised weakness and left-sided chest discomfort since 2 - 3 days. On further history taking there was no fever, sweating, palpitation, black stools or fresh blood in stools. He had no medication or recent vaccination history, did not consume alcohol and did not have any addictions. He had no history of any recent or past illness, such as tuberculosis, COVID. On examination, he was conscious, oriented general examination was normal, and vitals were stable. Rest of systemic examination was normal. With a probable diagnosis of acute gastroenteritis, relevant investigations were sent and treatment started with empirical antibiotics, i.e., inj Ceftriaxone (1 gm IV BD), inj Metronidazole (500 mg in 100 ml ns IV TDS), IV fluids and supportive treatment. Ultrasonography of whole abdomen and chest X-ray were performed, which were normal. Stool examination, LFT,

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KFT, coagulation profile and D-DIMER were normal. However, patient's full blood count showed severe isolated thrombocytopenia (Platelet: 5,000/mm3) with a normal haemoglobin (14.1gm/dl) and normal TLC (8,000/mm2) with normal differential leukocyte count. Further work-up for the cause of thrombocytopenia was done and hematologist reference was taken. Since Dengue is endemic to Delhi during monsoon month of September, Dengue Serology and NS1 antigen were tested as a probable cause of thrombocytopenia which came out to be negative. Further Typhi dot Ig M, WIDAL test, peripheral smear for malaria, malarial serology, urine and blood cultures were negative. Urine routine was normal with no proteinuria, hematuria. Acute phase reactants like ESR, CRP and Ferritin were also within normal limits ruling-out macrophage activation syndrome. Serum Vit B12, Folic acid, Homocysteine, and Iron study were normal. Peripheral smear was otherwise normal except marked thrombocytopenia. Indirect and direct coombs test were negative. HIV, hepatitis C, ANA titre, and lupus anticoagulant were negative. Conservative treatment was continued and platelets were arranged but not transfused as yet, due to absence of any bleeding manifestations. Patient's platelet counts were repeated, which further reduced to 2,000/mm^3 on next day, and he was then transfused 3 unit of RDP (random donor platelets) and 4 units of SDP (single donor platelet) over 2 days. He responded to the platelet transfusion and his platelet increased to 58,000/mm^3 on 3rd day. After consultation with hematologist and explaining risk of procedure to patient and relatives, a bone marrow aspiration (BMA) was done to know the cause of thrombocytopenia. The procedure was uneventful and BMA was reported as a normal reactive bone marrow with normal cell lines. His platelet count reduced further to 30,000/mm^3 on 4th day. Taking all results into consideration and hematologist consultation, a diagnosis of ITP was made. The patient was started on IV Solumedrol pulse therapy (500 mg IV OD*3 days) and T. Revolade (Eltrombopag 50 mg OD). Patient responded well to the treatment and his platelet count started showing a gradual increase and he was discharged on 5th day with a platelet count of 72,000/mm^3 on Tab. Wysolone 60 mg OD, Tab. Revolade 50 mg HS and supportive treatment. Patient was called for review after 5 days, and he presented with severe band like pain in abdomen equally on both sides radiating to the back since 1 day associated with nausea but no vomiting. There was no history of constipation. On examination, the vitals were stable, abdomen was tender and distended and bowel sounds were reduced. All other examination was normal. An urgent X-ray abdomen erect and supine was done to rule-out intestinal obstruction, and a surgery reference was sought.

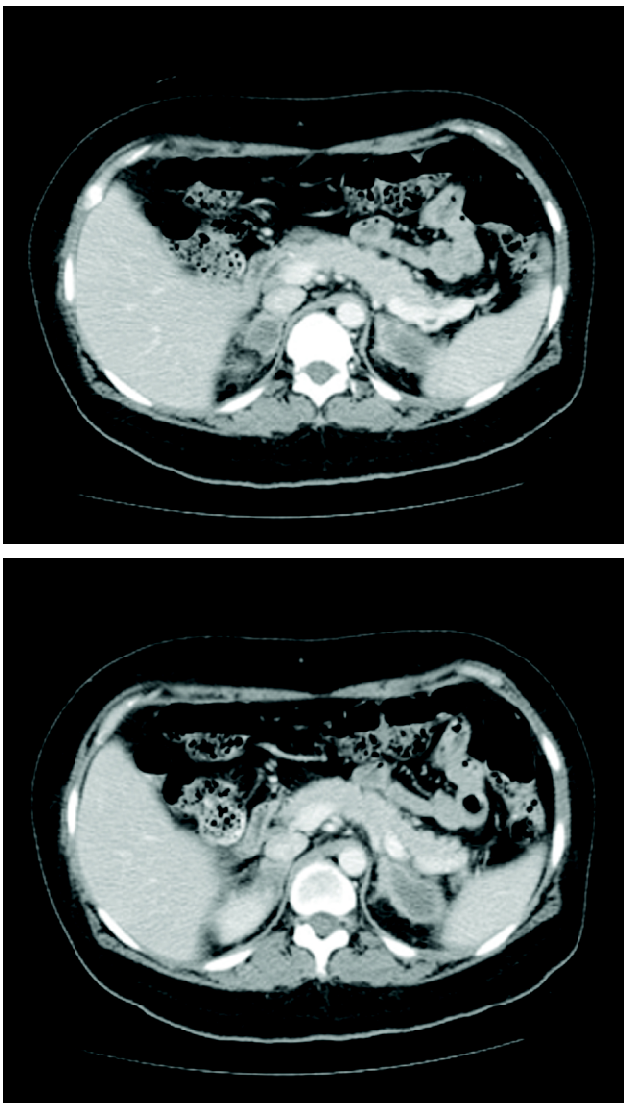

Fig. 1: *Bilateral adrenal haemorrhage on CECT scan of abdomen.*

Liver and Kidney function tests and urine reports were normal and fever profile was negative. Patient's platelet counts on admission were 28000/mm3 while taking Tab. Wysolone 60 mg OD and Tab. Revolade 50mg HS. Patient's USG of the abdomen showed bulky bilateral adrenals with adrenal hemorrhage and extensive surrounding inflammation. Also, there was minimal non-tappable bilateral pleural effusion and mild pericardial effusion. Further, on discussion with the hematologist, patient was suspected to have ITP induced BAH. A contrast enhanced CT scan of the abdomen was performed, which confirmed the diagnosis of BAH. Suspecting a complication of Addison's crisis the following blood tests were ordered, Serum ACTH, Cortisol (8 am) and 24-hr urinary cortisol. Of this Serum ACTH was high (75 pg/ml); all other tests were normal. Also, the patient's vitals electrolytes and blood sugar

levels were normal throughout the admission. On discussion, the steroid therapy given to the patient for ITP, prevented a full-blown adrenal crisis and haemodynamic instability. He was discharged on T. Fludrocortisone (100 mcg thrice a day dose), Tab. Wysolone 60 mg OD, Tab revolade 50 mg twice a day along with iron, vitamin B complex and folic acid supplementation. On subsequent follow-up, the BAH showed gradual resolution. Patient remained haemodynamically stable and showed gradual improvement. There was no clinical or radiological evidence of any arterio-venous thromboembolism. Written informed consent was taken from the patient to report this case with images.

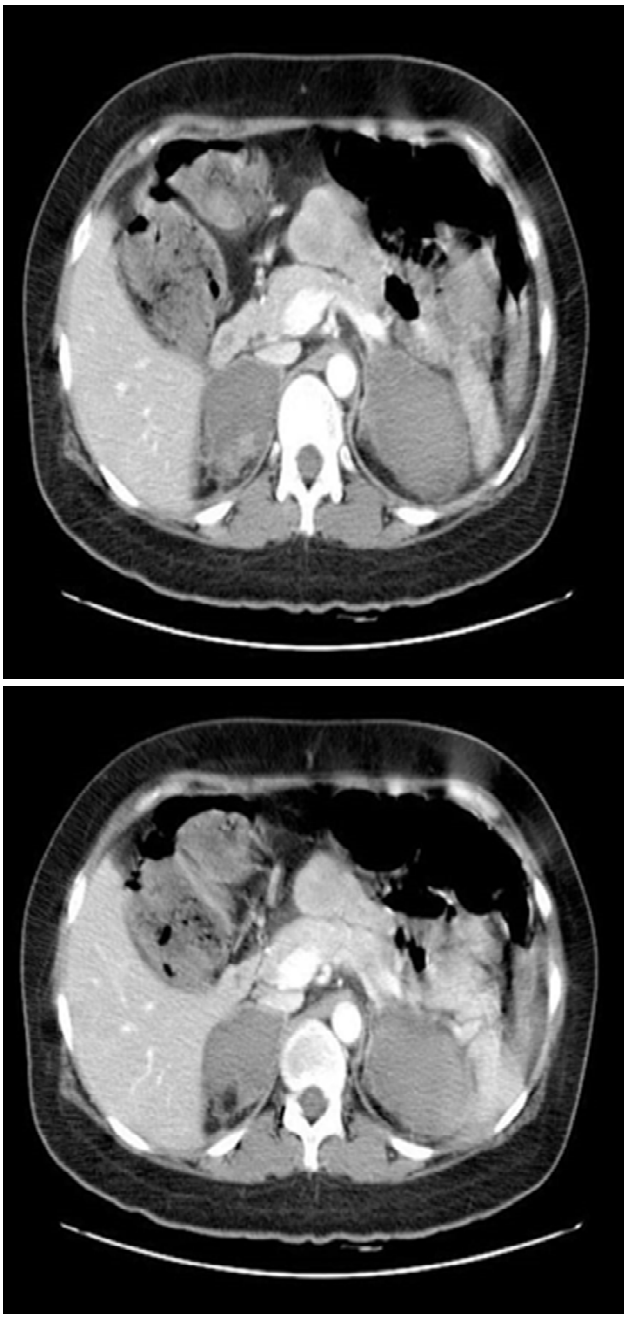

Fig. 2: *Follow-up study revealing decreased size of bilateral adrenal haemorrhage.*

Table I: Investigations on 1st admission

1st Admission	Day 1	2	3 (2 RDP, 1 SDP transfused)	5 (2 RDP, 1 SDP transfused)	7 (2 SDP transfused)
Haemoglobin (13.5 - 15 g/dl)	14.1	14	13.9		13.9
WBC (4 - 11 x 10^3/mm^3)	8,000	12,000	11,000		10,500
Platelet count (per mm^3)	2,000	2,000	15,000	58,000	72,000
INR (0.90 - 1.20)	1.12		1.2		1.0
S creatinine (0.7 - 14 mg/dl)	1.12	1.30	0.9		0.9
S urea (12 - 20 mg/dl)	20		18		15
D-DIMER (< 250 ng/ml)	120				110
S. TSH (0.47 - 4.68 mU/L)	1.34				
NS1 antigen	Negative				
Dengue serology	Negative				
S. Ferritin (6.2 - 137 ng/ml)	120				
S. LDH (120 - 246 U/L)	250				225
CRP (< 0.3 mg/dl)	0.2				0.2
ESR (0 - 22 mm/hr)	30				
S. Procalcitonin (0 - 0.50 ng/ml)	0.1				

Table II: Investigations on 2nd admission.

2nd Admission	Day 1	2	3	5	9
Haemoglobin (13.5 - 15 g/dl)	9.0	9.8	9.1		10.
WBC (4 - 11 x 10^3/mm^3)	8,000	12,000	11,000		10,500
Platelet count (per mm^3)	28,000	50,000	54,000	58,000	98,000
INR (0.90 - 1.20)	1.3		1.1		1.1
D-DIMER (<250 ng/ml)	400				245
S. TSH (0.47 - 4.68 mU/L)	1.34				
S. Ferritin (6.2 - 137 ng/ml)	144				
S. LDH (120 - 246 U/L)	300				
CRP (<0.3 mg/dl)	0.2				
ESR (0 - 22 mm/hr)	50				

Discussion

BAH is a rare condition, with an incidence of around 0.14 - 1.8%, mainly based on postmortem studies[1]. This rare clinical entity is associated with burden of potentially life-threatening consequences, due to acute adrenal insufficiency[2]. A major reason for poor outcome of this condition is that despite treatment with stress-dose glucocorticoids, many cases of adrenal haemorrhage die because of delayed recognition and treatment. A high

mortality rate of up to 15% has been reported; but it varies widely depending on severity of the underlying illness and is exponentially higher if the adrenal insufficiency is not diagnosed and treated promptly[1]. Pathophysiology of BAH is uncertain in most cases. Cortisol has multiple endocrine and metabolic functions, especially during stressful events. Adrenal haemorrhage due to stress is thought to be an exacerbation of the physiological effect of increase in arterial blood flow of adrenals alongwith slowing of venous drainage due to single adrenal vein, causing vascular congestion inside the glands leading to subsequent haemorrhage[2,3]. These physiological changes may be because of multiple predisposing factors, like stress from surgery, sepsis, severe illness, haemorrhagic diatheses (e.g., anticoagulants, thrombocytopenia), burns, thromboembolic disease like antiphospholipid antibody syndrome, etc.[2,7]. Adrenal haemorrhage is not usually suspected and hence missed due to nonspecific clinical and laboratory findings. It presents with non-specific signs of abdominal pain, fever, vomiting, weakness, hypotension or shock and altered sensorium, which are often same as those of the underlying illness making suspicion of adrenal haemorrhage very difficult[3]. Fever is one of the most common physical signs occurring in upto about 70% of cases[2] whereas hypotension is missed until it presents as shock[2,3]. Due to those difficulties, primary adrenal insufficiency secondary to adrenal haemorrhage, in the past, was diagnosed on post-mortem[3,7]. Likewise, in our case, abdominal pain, fever, and hypotension were misinterpreted as sepsis and intestinal obstruction. Also, laboratory findings are not invariably present, as the acute adrenal crisis was masked by the corticosteroid therapy the patient was already taking. Hyponatraemia, hyperkalaemia, and hypoglycaemia are commonly found in adrenal insufficiency but were absent in our case[3]. Although low serum sodium with high serum potassium is suggestive of underlying adrenal insufficiency, its absence cannot exclude this diagnosis[3]. Hormonal diagnosis is confirmed with serum cortisol and plasma ACTH. Acute adrenal insufficiency is diagnosed by combination of increased plasma ACTH and low or low normal <13 mcg/dl) serum cortisol. These are highly suggestive of glucocorticoid deficiency due to primary adrenal insufficiency caused Addison's crisis. The short synocthen stimulation test can also be used to confirm the diagnosis. Basal cortisol and ACTH levels are sufficient to start immediate glucocorticoid replacement therapy[2,3,7]. Recent literature describes the crucial role of imaging, especially CT scan, to confirm the diagnosis of adrenal haemorrhage. As both benign and malignant adrenal conditions may present with massive bleeding, or evolve in partially fluid lesions, it is difficult to differentiate it on basis of scans. But a careful follow-up shows a typical decrease in volume of idiopathic haemorrhage in contrast to neoplasms, which do not decrease in size with time[2]. Furthermore, adrenal haemorrhage should also be suspected when there is ill-defined soft-tissue stranding around adrenal gland, due to infiltration of blood through retroperitoneal fat . In the acute phase, the patient should

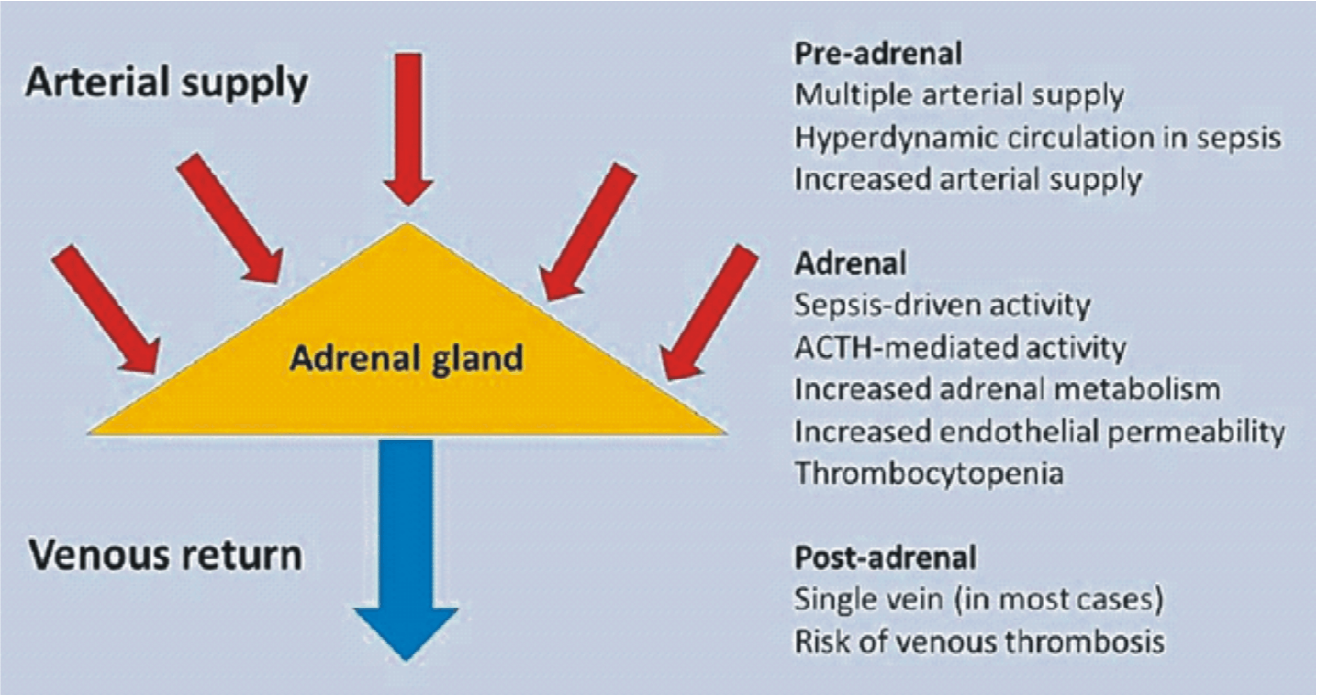

Fig. 3: *Schematic diagram showing the possible mechanisms involved in spontaneous adrenal haemorrhage (ACTH, adrenocorticotropic hormone).*

be immediately treated with hydrocortisone (initially 100 mg intravenous bolus followed by 200 - 300 mg over 24 - 48 hours as continuous infusion) and isotonic saline (1,000 ml within the first hour). After the acute management, long-term glucocorticoid replacement, preferably with mineralocorticoid replacement therapy is necessary, based on the results of adrenal function test[3,4].

ITP is caused by platelet destruction due to immune-mediated mechanisms and inadequate platelet production. ITP is classified based either on duration (acute or chronic) or age (childhood or adult).

Diagnosis of ITP is made by exclusion of other causes of isolated thrombocytopenia. Also, secondary causes of thrombocytopenia like leukaemia, HIV, hepatitis C, congenital causes, drugs and others must be excluded[1]. American Society of Hematology, states that a diagnosis of ITP can be made principally by history, physical examination, haemogram, peripheral smear examination and ruling-out other possible causes of thrombocytopenia[8].

Signs and symptoms of ITP are very variable and can range from the common presentation of an asymptomatic patient with mild mucosal bleeding (e.g., oral or gastrointestinal tract bleeding) or mild bruising to frank bleeding from any site or organ. Symptomatic bleeding is usually uncommon in ITP until severe thrombocytopenia occurs (platelet count <30,000/μl). However there is a poor correlation between severity of thrombocytopenia and bleeding manifestations. Severe cutaneous bleeding, menorrhagia, prolonged epistaxis, gingival bleeding, overt hematuria can develop even at platelet counts more than 10,000/μl[1].

Our case seems to be the first presentation of thrombocytopenia, and despite the low platelet count it was surprising that he has not had any episode of bleeding during the 1st admission. In the adult patient, ITP is generally insidious in onset without preceding illness and has a chronic course, unlike the pediatric population where it tends to follow the illness by a few days to a few weeks[9]. The temporal course of the illness in the case is more like an acute ITP, but the absence of bleeding is surprising given the severity of thrombocytopenia and rapid fall in platelet count in-hospital[10].

Immediate therapy is not indicated for patients with platelet counts between 20,000 and 50,000/μl, with on bleeding or predisposing comorbid conditions such as hypertension, anticoagulation, or recent surgery[1]. In patients with severe ITP, the aim is to increase platelet count immediately above 30,000/μl to prevent any lethal bleeding symptoms because thrombocytopenia in a patient with a platelet count less than 30,000/μl is associated with an exponentially increased mortality risk compared with thrombocytopenia in a patient with a platelet count more than 30,000/μl[11]. Therefore, especially in patients with severe ITP, rapidly increasing the platelet count is crucial. First-line therapy consists of corticosteroids, IVIg or other therapies. High-dose IV immunoglobulin therapy is considered first-line in bleeding emergencies of as it quickly improves symptoms. The small but increased risk of thrombosis in ITP patients has been attributed to patient related factors, treatment related factors, disease pathophysiology and presence of anti-phospholipid antibodies[12,13], but such complications were not seen with our case and he tolerated treatment well. The change in the bleeding phenotype to thrombotic may be due to platelet microparticles and young platelets in circulation along with endothelial activation with activation of natural anti-coagulation pathways and complement activation. In most patients with thrombosis in the setting of ITP treatment post-splenectomy status, patient factors and anti-phospholipid antibodies have been found to be significant. Practically all classes of drugs have been implicated in thrombosis including corticosteroids, IVIG, Thrombopoietin receptor agonists and anabolic steroids.

In conclusion, in spite of an ambiguous initial presentation of adrenal insufficiency, particularly when it overlaps with other manifestations of the concurrent severe illness, an early diagnosis is crucial to avoid catastrophic consequences of adrenal crisis. Therefore, this diagnosis requires a high index of clinical suspicion and rapid confirmation with CT of the abdomen. It is essential to identify early signs of adrenal congestion, such as gland thickening with surrounding fat stranding, a careful monitoring of the patient and eventually prompt replacement glucocorticoid therapy.

Conclusion

Our patient, a 48-year-old man, was diagnosed as ITP, secondary to acute infective gastroenteritis for which treatment was started with platelet transfusion and corticosteroids. Thereafter, patient developed spontaneous BAH secondary to ITP; the complications of adrenal crisis prevented by ongoing steroid therapy. Patient was managed with hydrocortisone followed by regular follow-up which revealed evolution of the BAH over time. This case emphasizes the importance of heightened awareness and clinical suspicion of this life-threatening condition.

References

1. Kovacs K, Lam Y, Pater J. Bilateral massive adrenal haemorrhage: assessment of putative risk factors by the case control method. *Medicine (Baltimore)* 2001; 80: 45e53.
2. Kawashima A, Sandler CM, Ernst RD *et al*. Imaging of non traumatic haemorrhage of the adrenal gland. *Radiographics* 1999; 19 (4): 949e63.

3. Rao RH, Vagnucci AH, Amico JA. Bilateral massive adrenal haemorrhage: early recognition and treatment. *Ann Intern Med* 1989; 110 (3): 227e35.
4. Jordan E, Poder L, Courtier J *et al*. Imaging of nontraumatic adrenal haemorrhage. *AJR Am J Roentgenol* 2012; 199 (1): W91e8.
5. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005; 106: 2244-51.
6. Sangwan A, Tewari S, Narula SC *et al*. Significance of periodontal health in primary immune thrombocytopenia: a case report and review of literature. *J Dent (Tehran)* 2013; 10: 197-202.
7. Siu SC, Kitzman DW, Sheedy 2nd PF. Adrenal insufficiency from bilateral adrenal haemorrhage. *Mayo Clin Proc* 1990; 65 (5): 664e70.
8. Neunert C, Lim W, Crowther M *et al*. American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117: 4190-4207.
9. Provan D, Stasi R, Newland AC *et al*. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115 (2): 168-86.
10. Rand ML, Wright JI. Virus-associaled idiopathic thrombocytopenlc purpura. *Tranfus Sci* 1998; 19 (3): 253-9.
11. Portielje JE, Westendorp RG, Kluin-Nelemans HC. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001; 97: 2549-54.
12. Tărniceriu CC. Hurjui LL, Florea ID *et al*. Immune Thrombocytopenic purpura as a Haemorrhagic Versus Thrombotic Disease: An Updated Insight into Pathophysiological Mechanisms. *Medicina (Kaunas)* 2022; 58 (2): 211.
13. Swan D, Newland A, Rodeghiero F. Thrombosis in immune thrombocytopenia-current status and future perspectives. *Br J Haematol* 2021; 194: 822-34.