

Life-Threatening Wunderlich Syndrome Associated with Apixaban and the Complexity of Anticoagulation Management in Bleeding Patients: A Case Report

Síndrome de Wunderlich Associada ao Apixabano e à Complexidade de Gestão de Anticoagulação em Doentes com Hemorragia: Um Caso Clínico

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ABSTRACT

Wunderlich syndrome is a rare and possibly life-threatening haemorrhagic syndrome presenting as spontaneous nontraumatic renal rupture with subcapsular and perinephric haemorrhage. Apixaban, a direct oral anticoagulant recommended in patients with atrial fibrillation, has previously been associated with atraumatic solid organ rupture but, to date, no case of apixaban-related Wunderlich syndrome has been reported. We report a rare case of Wunderlich syndrome associated with apixaban while addressing the difficulties face by clinicians when managing anticoagulation in bleeding patients.

Keywords: Acute Kidney Injury; Anticoagulants/adverse effects; Hemorrhage; Kidney Diseases/chemically induced; Rupture, Spontaneous

RESUMO

A síndrome de Wunderlich é uma síndrome hemorrágica rara caracterizada por rutura renal espontânea, não-traumática, com hemorragia subcapsular e peri-renal. O apixabano, um anticoagulante oral direto recomendado em doentes com fibrilação auricular, foi associado no passado a rutura atraumática de órgãos sólidos mas, à data, nenhum caso de síndrome de Wunderlich associada ao apixabano foi reportado. Reportamos um caso raro de síndrome de Wunderlich associada ao apixabano abordando concomitantemente as dificuldades na gestão da anticoagulação em doentes com hemorragia.

Palavras-chave: Anticoagulantes/efeitos adversos; Doenças do Rim/induzida quimicamente; Hemorragia; Lesão Renal Aguda; Ruptura Espontânea

INTRODUCTION

Direct oral anticoagulants (DOAC) are associated with spontaneous haemorrhage and, in rare cases, atraumatic solid organ rupture.^{1,2} Yet, to date, no reports exist of renal rupture, or Wunderlich syndrome (WS), associated with DOAC use. To the best of our knowledge, we present the first-ever case report of WS associated with apixaban while highlighting the difficulties clinicians face in managing patients with a high-bleeding and high-thrombotic risk.

CASE REPORT

A 79-year-old female with a medical history of permanent atrial fibrillation (AF) diagnosed two years prior and currently under apixaban and previous right (seven years ago) middle cerebral artery (RMCA) stroke was admitted to the emergency department due to sudden and intense left-flank pain. She denied fever, chills, night sweats, dysuria, supra-pubic/abdominal pain or trauma. She did not have any known clotting/bleeding disorders. Vital signs were stable and the physical examination only revealed abdominal tenderness. Blood tests showed a hemoglobin of 9.2 g/dL (down from a baseline of 11.1 g/dL 12 months prior), platelet count $188 \times 10^9/L$, creatinine 2.05 mg/dL (up from a baseline of 0.85 mg/dL) and c-reactive protein of 5.0 mg/dL. Urinalysis revealed numerous leucocytes. An initial diagno-

sis of acute pyelonephritis was assumed, and the patient was discharged with antibiotics and paracetamol for pain management.

Six hours later she developed new-onset obtundation, leading to re-admission to the emergency department. The patient was now hypotensive, lethargic and blood gas analysis showed mixed acidemia with a pH of 6.9 (reference value: 7.35 - 7.45), pCO₂ 76 mmHg (reference value: 35 - 45 mmHg) and lactate of 13.0 mmol/L (reference value: < 2.0 mmol/L). The blood tests also revealed a hemoglobin of 6.4 g/dL (reference value: 12.0 - 15.0 g/dL), an international normalized ratio (INR) of 1.2 and creatinine of 3.31 mg/dL (reference value 0.50 - 0.90 mg/dL). Therefore, a diagnosis of hemorrhagic shock was assumed. The patient was transferred to an intensive care unit for vasopressor support, orotracheal intubation and mechanical ventilation. Apixaban was suspended and the presumed volume loss replaced with 2000 mL of normal saline followed by three units of packed red blood cells, after which hemodynamic stability was achieved. A contrast-enhanced abdominopelvic computed tomography (CT) was ordered, revealing an upper-left renal rupture with extensive perirenal hemorrhage (Figs. 1 and 2), without active contrast extravasation. Therefore, a diagnosis of WS was made. The CT showed

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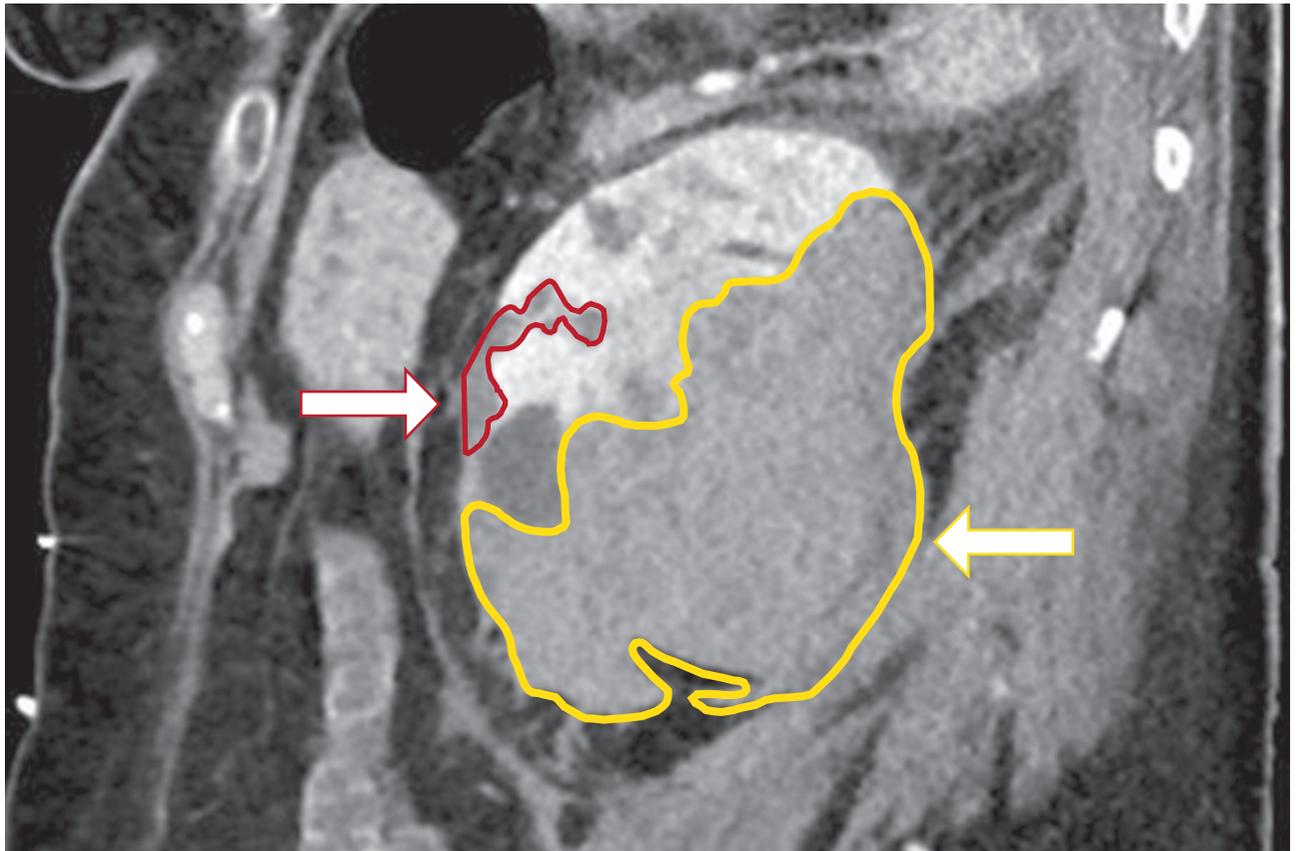


Figure 1 – Abdominal computed tomography (sagittal plane) revealing extensive left perirenal haemorrhage (yellow outline; yellow arrow) and left upper renal rupture (red outline; red arrow)

no renal masses or malignant lesions. Due to hemodynamic stability after blood transfusion, she was managed conservatively with bed rest and surveillance. A follow-up CT scan was done before discharge, showing significant renal subcapsular hematoma reabsorption and no parenchymal disease.

On day seven of admission, at a time when anticoagulation was still suspended, the patient woke up with nausea and left-arm paresis, with a National Institute of Health Stroke Scale (NIHSS) score of 5. A cranial CT confirmed a RMCA M2-segment occlusion, left vertebral artery occlusion and subacute left cerebellar infarction. Intravenous thrombolysis was contraindicated due to recent life-threatening bleeding. Given the low NIHSS score, distal-vessel occlusion and need of periprocedural heparin, mechanical thrombectomy was discarded after multidisciplinary discussion, including intensive care/internal medicine/neurology/neuroradiology consultation. The patient was therefore started on a single-antiplatelet strategy with aspirin and apixaban remained suspended. Yet, a follow-up cranial CT scan showed a new right posterior cerebral artery infarction and hemorrhagic transformation of a previous cerebellar infarction. Therefore, anticoagulation was again consid-

ered prohibitive and aspirin was maintained. After a third cranial CT scan revealed complete cerebellar hemorrhage reabsorption and no other bleeding events, anticoagulation resumption was deemed safe. Finally, on day 47 of admission, the patient was discharged on apixaban to a short-term physical-rehabilitation facility, with ongoing improvement of neurological deficits and normal renal function.

DISCUSSION

WS is a rare and possibly life-threatening disease defined by non-traumatic renal haemorrhage.³ Patients may present a classic ‘Lenk’s triad’ comprising of sudden or insidious flank/abdominal pain, palpable flank mass and hypovolemic shock.⁴ Renal neoplasms (e.g. angiomyolipoma or renal cell carcinoma) are the most frequent aetiologies and underly WS in up to 60% of patients.³ In rare situations no cause is found.⁴ Contrast-enhanced CT has 100% sensitivity in identifying perirenal haemorrhage and is the standard imaging technique in diagnosing WS.⁵ CT can also assess renal vasculature, neoplasms or other structural changes that may underly WS.⁵ During our patients’ assessment, CT scan did not show any renal lesions concerning neoplasms nor parenchymal/vascular renal disease. Moreover, her

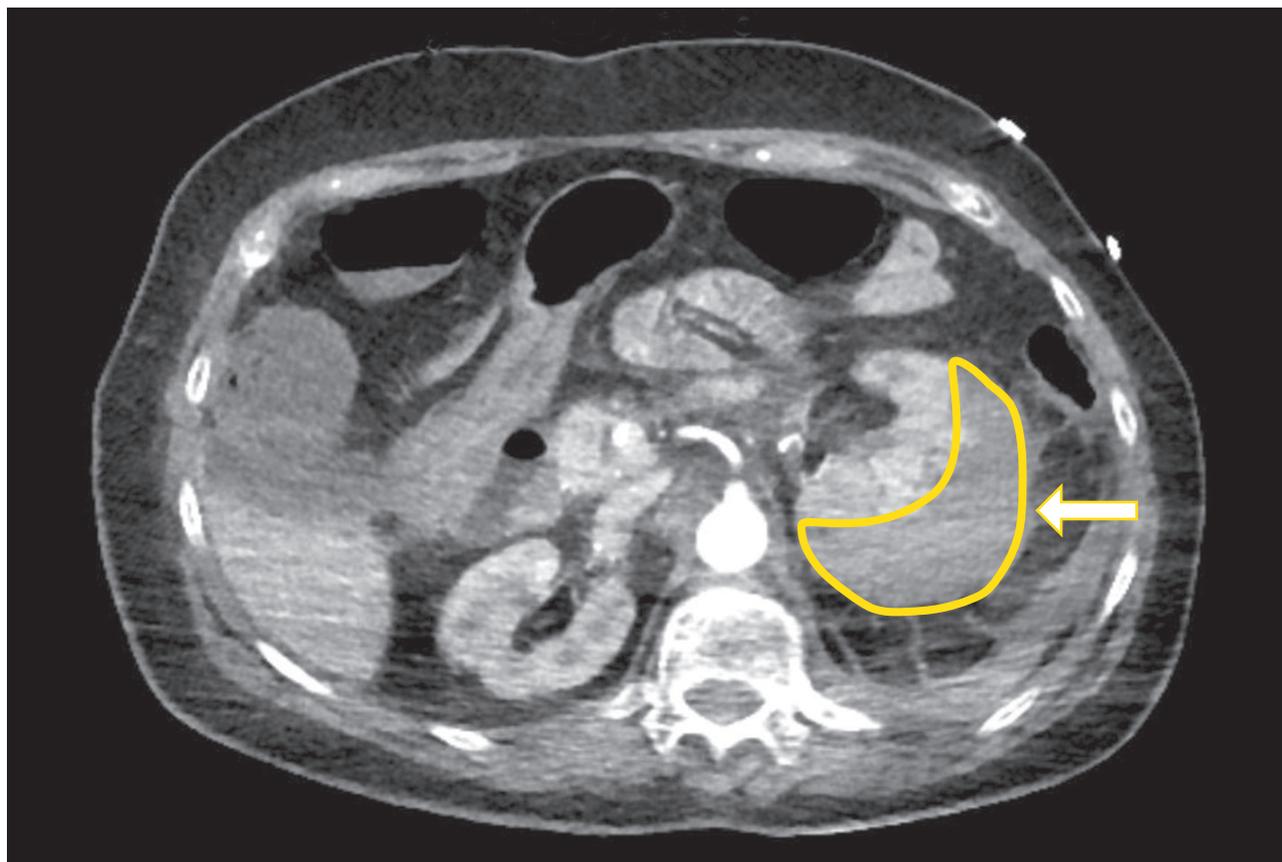


Figure 2 – Abdominal computed tomography (transverse plane) with extensive left perirenal haemorrhage (yellow outline; yellow arrow)

past medical history, current symptoms and baseline blood and urine tests did not point to any other possible causes of WS (e.g. vasculitis, nephritis or coagulation disorders).

Currently, no guidelines for WS management exist.⁶ Treatment should rely on anticoagulation discontinuation/reversal, immediate fluid resuscitation and angioembolization or emergent nephrectomy in clinically deteriorating patients.⁶ Due to scarcity of cases, optimal management is controversial. While some urologists favour early exploratory surgery or selective arterial embolization, others may prefer a more conservative approach.⁷ Indeed, some authors recommend radiological re-evaluation following hemodynamic stability to avoid unnecessary nephrectomy.⁸

Apixaban is a DOAC and a reversible inhibitor of free and clot-bound forms of activated factor X.⁷ In the ARISTOTLE trial, apixaban was superior to warfarin in reducing the risk of stroke or systemic embolism in nonvalvular AF while also causing less bleeding events and lowering overall mortality.⁹ Therefore, current European Society of Cardiology AF guidelines recommend apixaban and other DOACs over warfarin in the majority of patients with nonvalvular AF.¹⁰ Despite DOACs' superior safety, several case reports of atraumatic solid-organ rupture, mainly spontaneous splenic

rupture, still exist.^{1,2} To our knowledge, no reports of WS associated with apixaban have been published.

Concerning thromboembolic prevention after a major bleeding event, guidelines provide limited guidance regarding the optimal timing for anticoagulation resumption. Indeed, our patient developed multiple embolic strokes seven days after anticoagulation cessation. Due to hemorrhagic transformation, apixaban resumption was contra-indicated.

Our case highlights the importance of prompt consideration of renal or intra-abdominal haemorrhage in all anticoagulated patients presenting with new-onset flank pain, raised creatinine levels and declining haemoglobin levels, even in the absence of an obvious trauma. Moreover, this case underlines the importance of an urgent imaging study among those presenting with acute kidney injury and abdominal or flank pain in the emergency department. It also emphasizes the challenging decision of restarting anticoagulation after a life-threatening bleeding event. Given the absence of clear guidelines, the decision to resume anticoagulation should be individually tailored.

CONCLUSION

To our knowledge, we present the first-ever case report

of WS associated with DOAC. WS is a rare and potentially life-threatening event. A high level of suspicion must be maintained in all patients presenting with flank pain and haemorrhagic shock, especially in those under anticoagulants or platelet-inhibitors. Management of patients with active bleeding while on DOAC is complex, particularly when simultaneous thromboembolic events occur. This case highlights the difficulties faced in deciding the appropriate timing to resume anticoagulation in patients with severe haemorrhage.

AUTHOR CONTRIBUTIONS

SM: Draft of the paper.

CCG, FS, MR: Draft and critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declara-

tion of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors declare that there are no competing interests.

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