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CASE REPORT

Unexpected High International Normalised Ratio

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ABSTRACT

45-year-old man who was suspected to have the antiphospholipid syndrome, presented with persistently high international normalised ratio despite not being on any oral anticoagulant. He was previously put on Rivaroxaban at another institution after multiple episodes of thromboembolic events, but was stopped prior to his admission at our clinic. No bleeding episodes were recorded. Subsequent measurements of prothrombin time (PT) were performed using Sysmex CS-2500, Sysmex CA-104 and Instrumentation Laboratory (IL) ACL Top analysers. PT results by both Sysmex analysers were prolonged at 34s and 30s, respectively. Conversely, the PT result using IL ACL Top analyser was within normal range. Both Sysmex analysers used a PT reagent, which incorporated a recombinant thromboplastin. When PT was repeated using a tissue derived PT reagent, PT result was within the reference range. The patient was later found to have antiphospholipid antibodies with triple positivity.

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disorder, associated with antiphospholipid antibodies, such as lupus anticoagulant (LA), anti-cardiolipin antibody and anti-B2 glycoprotein 1. Thrombotic events are reported in approximately 30% of patients with antiphospholipid antibodies [1], with an overall incidence of 2.5% of patients/year [2]. LA is a non-specific coagulation inhibitor. It may cause in vitro prolongation of phospholipid-dependent clotting time such as the activated partial thromboplastin time (aPTT) and less commonly, prothrombin time (PT). We present a case of a persistently high international normalised ratio (INR) despite not being on warfarin treatment. The abnormal INR results were reflected in the consistently high PT results.

CASE PRESENTATION

A 45-year-old man with a history of mitral valve replacement and multiple episodes of thromboembolic events was referred to our institution for neurological rehabilitation. He was on Rivaroxaban as secondary stroke prevention before his presentation. Based on his clinical history, he was suspected of having antiphospholipid syndrome and the clinician planned to start warfarin treatment. Blood samples were sent routine blood tests and antiphospholipid antibodies. Rivaroxaban was changed to subcutaneous Clexane temporarily before starting on warfarin. His initial blood test results showed a haemoglobin level of 11g/dL

(Reference Interval (RI): 13g/dL-17g/dL) and a platelet count of 81x109/L (RI: 150-410x109/L). However, his coagulation profile prior to starting any anticoagulant, was abnormal, with a PT of 80.5s, aPTT of 48.3s and INR of 8.5. He was then admitted to the hospital for further investigation. During his admission, his mean Hb was 11g/dL (min= 9.7g/dL, max=12g/dl). His serial full blood count results are shown in Table 1.

Table 1 Serial full blood count results

	January 2022											Feb 2022		March 2022		Apr 2022	May 2022
Date	5	6	7	8	10	11	12	13	20	24	28	24	2	9	15	14	12
Hb (g/dl)	10.9	10.6	11.7	12	9.7	9.7	10.1	11.7	10.8	11.1	10.9	11.4	10.7	11.4	11	11.6	11.4
Plt ($x10^9$/L)	59	59	78	93	65	61	63	84	109	127	113	102	99	90	99	90	108

The platelet counts remained consistently low within the first 2 weeks of admission, without any bleeding tendency. His coagulation study was repeated a few times over the next few days. The mean PT, aPTT and INR were 48.7s, 35s and 5.0, respectively (RI: PT= 10.5s–12s, aPTT= 22.2s – 33s). A mixing test for PT was performed due to the markedly abnormal results and showed non-correction. His factor VII level was 78.4% and no FVII inhibitor was detected. The samples were sent to an external laboratory, which reported slightly raised PT and INR results of 13.8s and 1.8, respectively. An investigation into the cause of the unexpected prolonged PT was conducted at both laboratories, using different analysers and reagents. Sysmex CS-2500 were used at our laboratory to run all routine coagulation testing. The PT, aPTT and INR results at the external laboratory, which were analysed using ACL Top analyser by Instrumentation Laboratory (IL) and HemosIL (reagent), were reported to be within normal range. The Sysmex CA-104 was also used to analyse the same blood sample. The PT reagent used for both Sysmex analysers was Dade Innovin. The results are shown in Table 2. Two weeks later, another sample was tested using a new lot of Dade Innovin reagent and another PT reagent, Thromborel S. The results are shown in Table 3.

Table 2 Results of PT, aPTT and INR using 3 different analysers and reagents

	PT (s)	aPTT (s)	INR
CS-2500/ Dade Innovin	40.5	34.7	4.1
CA-104/ Dade Innovin	56	30	NA*
ACL Top/ HemosIL	13.4	58.1	1.2

*NA – Not Available

Table 3 Results of PT, aPTT and INR using Sysmex CS-2500 and 3 different reagents

Analyser/ Reagent	PT (s)	aPTT (s)	INR
CS-2500/ Dade Innovin	41.3	34.3	4.2
CS-2500/ Dade Innovin (new lot)	37.9	NA*	4.34
CS-2500/ Thromborel S	13.1	NA*	1.1

*NA – Not Available

PT reagent was changed to Thromborel S and warfarin was started. However, due to the time taken to establish the new mean normal PT (MNPT) for Thromborel S, his PT and INR levels were measured using Stago STA Compact, which uses a mechanical viscosity-based detection system. The mean PT and INR using the STA Compact, were 23.1s and 1.8, respectively. The results of lupus anticoagulant, anti-cardiolipin antibody and anti-B2 glycoprotein came back as triple positivity. However, he defaulted his clinic appointment and lost to follow-up 6 months after his first presentation to our institution.

DISCUSSION

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboembolic events with or without pregnancy complications, in the presence of persistent antiphospholipid (aPL) autoantibodies including lupus anticoagulant (LA), anticardiolipin (aCL) and anti-beta2 glycoprotein (anti-β2GPI) autoantibodies [3]. The first classification was devised in Sapporo in 1999 and updated in 2006 in Sidney as the revised Sapporo Classification Criteria. Lupus anticoagulant is a non-specific plasma inhibitor. It causes in vitro prolongation of phospholipid based coagulation tests such as aPTT and less commonly, PT. PT is rarely affected by lupus anticoagulants because of the high concentration of phospholipid in the reagent thromboplastin. LA is associated with thrombosis, however, bleeding may also occur when associated with hypoprothrombinaemia [4].

Sysmex CS-2500 is a mid-volume, fully automated coagulation analyser that uses the photo-optical method. The analyser detects clot formation by measuring the change in optical density (OD) of a test sample. As the plasma sample clots, it becomes more optically dense and the light transmittance decreases. The drop or change in light transmittance is determined as the endpoint of coagulation [5]. IL ACL Top also uses the same principle. However, the results of PT and INR of both analysers were markedly different. The results were within the normal range for ACL Top but for CS-2500, the results were above the normal range. The INR was supratherapeutic when analysed using CS-2500, which was incorrect given the patient was not taking warfarin.

INR is derived from PT ratio using the formula below:

$INR = [PT\ (patient)/\ PT\ (normal)]^{ISI}$ ISI = international sensitivity index

PT reagents contain thromboplastin as a source of tissue factor and phospholipids. Thromboplastin can be extracted from brain or placental tissue, or it can be recombinant. The addition of the PT reagent to the patient's plasma in the presence of calcium ions initiates the activation of the extrinsic pathway. The use of different kinds of thromboplastin leads to varying sensitivity of the PT reagents to the reductions in the levels of vitamin K-dependent clotting factors. These variations have been standardised using the international sensitivity index (ISI) and international normalized ratio (INR) [6]. HemosIL RecombiPlasTin 2G was used as a PT reagent by the ACL Top analyser at the external laboratory in this case report. It was formulated based on recombinant human tissue factor (RTF), to be used specifically with ACL Top. Our laboratory used Dade Innovin® as the PT reagent for the Sysmex CS-2500 analyser. This reagent also contains recombinant thromboplastin. However, the results of PT, aPTT and INR produced by both systems were markedly different, which could be caused by the unique composition of both reagents or sensitivity of the reagents towards the anti-phospholipid antibodies [7]. The other PT reagent for the CS-2500 analyser, Thromborel®S, contains placental tissue extract. The PT and INR results were similar to the ACL Top system. Evidence showed that the recombinant human thromboplastin is more sensitive to a reduction in FVII compared to tissue-extract thromboplastins [6, 8]. Factor VII (FVII) level was sent to exclude factor deficiency as a cause of prolonged PT. Even though there was no previous bleeding history to suggest a congenital factor deficiency, up to one-third of people with FVII never have any bleeding problems [9]. The mixing test was not corrected, which may suggest the presence of an inhibitor. However, the FVII level result was normal (78.4%) and there was no FVII inhibitor detected.

The results for LA, aCL and α-B2GPI came back positive for all three antibodies. Testing for LA was done while the patient was on Clexane. Studies have shown that clexane may prolong aPTT slightly but it should not affect LA testing using diluted Russell Viper Venom Time (dRVVT) [10].

Rivaroxaban caused thrombocytopenia in 2 reported cases, in which the platelet count improved rapidly after stopping the medication [11]. In our patient, his platelet counts did not improve very much after cessation of the drug and remained between 59x109/L to 127 x109/L (mean 89 x109/L), for 6 months. He was also mildly anaemic with a haemoglobin level ranging between 9.7g/dL and 12.g/dL (mean 11g/dL), which is probably due to his underlying chronic disease. This patient had mitral valve regurgitation secondary to rheumatic heart disease. He had multiple episodes of cerebrovascular accidents following mitral valve replacement.

Warfarin is a standard treatment for APS patients with prior thromboembolic events. It is a secondary antithrombotic prophylaxis with a target INR of 2.0–3.0 and should be taken lifelong [3]. The anticoagulant effect of warfarin can be monitored using INR. Several reports conclude that specific thromboplastin reagents containing recombinant tissue factors are sensitive to the presence of LAs and should not be used to monitor oral anticoagulant therapy in these patients [12].

CONCLUSION

In conclusion, cases of LA interfering with PT measurement using recombinant thromboplastin are rarely reported. We excluded FVII deficiency and FVII inhibitor as the causes of prolonged PT and raised INR. In our case, lupus anticoagulant, which is a non-specific inhibitor, reacted with Innovin, which is a recombinant thromboplastin, leading to abnormal PT/ INR results. Thus, we had to change to a tissue-derived PT reagent to allow INR to be used to monitor the anticoagulant effect in this patient. Unfortunately, the patient was lost to follow-up after 6 months. Nevertheless, this case illustrates how extensive troubleshooting can be, to ensure a reliable result can be given.

Consent

No consent was taken and the patient's identity has been kept anonymous throughout the writing of this case report. No picture of the patient was disclosed.

CONFLICT OF INTEREST

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare the absence of conflicting interests.

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AUTHORS' CONTRIBUTIONS

The authors confirmed contribution to the paper as follows: study conception and design, draft manuscript preparation: Fatmawati Kamal; data collection, analysis and interpretation of results: Halimatun Radziah Othman. All authors reviewed the results and approved the final version of the manuscript.

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