POINTS TO REMEMBER

- APS is a common cause of a prolonged APTT, but high titers of antiphospholipid antibodies may occasionally lead to a prolonged PT as well.
- The effect of antiphospholipid antibodies on APTT and PT may vary greatly between reagents from different manufacturers.
- Testing for antiphospholipid antibodies is indicated for any unexpected result in coagulation testing, when preanalytical causes have been excluded and results are not corrected in mixing studies.
- It is advisable to check the INR of the patient after discontinuing vitamin K antagonists in the same anticoagulation clinic where the patient is regularly seen.

This case shows that a strong presence of antiphospholipid antibodies can result in large heterogeneity of INR values, and may delay treatment and thereby increase healthcare costs. The influence of antiphospholipid antibodies on INR values is dependent on the reagent used by the clinical laboratory. Therefore, doubtful results in coagulation testing should always be discussed with a laboratory professional, as was done in this case by the patient himself.

CASE FOLLOW-UP

Colonoscopy was successfully performed after the patient stopped anticoagulant therapy for 3 days. The patient continued using a vitamin K antagonist for his APS.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

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Commentary

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This case highlights a rare but important source of interference in clot-based coagulation testing: prolongation of the prothrombin time (PT) and international normalized ratio (INR) by lupus anticoagulant (LA) autoantibodies. A PT reagent consists of $CaCl_2$ plus tissue factor protein and a phospholipid mixture, which together function as thromboplastin to activate factor VII and the extrinsic coagulation pathway. "Resistance" to LA interference is primarily due to the higher concentration of phospholipids in the PT reagents compared with activated partial

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thromboplastin time reagents. However, PT thromboplastins containing recombinant human tissue factor and proprietary phospholipid blends are more likely to be prolonged by some LA antibodies compared with PT thromboplastins derived from animal, typically rabbit brain, tissue, as demonstrated in this clinical case study. Falsely increased PT/INR values could lead to unnecessary transfusions of plasma or coagulation factor concentrates, or they could lead to subtherapeutic anticoagulation with vitamin K antagonists (VKA) like warfarin. How can laboratory directors protect patients from this interference and its serious potential consequences? First, they should select PT reagents verified to be LA-insensitive by the manufacturer, independent clinical studies, or within their own laboratory. Second, they should work to establish an institutional requirement for baseline PT/INR testing before initiating VKA therapy and monitor compliance as a patient safety quality indicator. Third, they should provide a PT mixing study test (1:1 patient plasma and pooled normal plasma) to investigate unexplained prolonged PT results. If PT is prolonged because of coagulation factor deficiencies, the PT mix results should completely or substantially correct. If PT is prolonged because of an inhibitor, the PT mix results may partially correct or not correct at all. Fourth, they should carefully investigate inquiries from patients or clinicians who question PT/INR results that are confusing, as was done by the alert laboratory directors who submitted this case study.

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Commentary

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Lupus anticoagulants (LA) are a heterogeneous family of immunoglobulins that interfere with negatively charged phospholipids and prolong the activated partial thromboplastin time *(1)*. The international normalized ratio (INR), used to monitor patients on vitamin K antagonists (VKA) *(2)*, is much less responsive to LA because thromboplastins used for INR testing typically contain excess amounts of phospholipids. There are, however, certain LA and/or thromboplastins that are subject to the interference *(3)*. This is very undesirable when patients are LA-positive and are on VKA. If the thromboplastin, which is responsive to VKA, is also responsive to LA, the two effects may be additive, making it difficult to assess the degree of anticoagulation achieved by a given VKA dosage. Based on observations designed to assess the clinical relevance of this effect *(3)*, it was concluded that there is no effect of LA on the INR for the majority of thromboplastins and patients. However, as reflected in this case, there may be exceptions. As preparation for an invasive procedure at a local hospital, this patient's VKA therapy was discontinued. A few days later, the patient's INR at this hospital was much higher than expected, calling into question whether the patient had genuinely stopped taking the VKA. On repeat testing, performed later on the same day in the anticoagulation clinic where the patient was usually monitored, the INR was much lower and compatible with VKA discontinuation. The contrasting results can be explained by the different responsiveness to LA of the thromboplastins used in the two laboratories. Patients on VKA undergoing temporary interruption of treatment for surgery or invasive procedures should have their INR measurement done at the same hospital (with the same thromboplastin) where they are usually monitored.

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