Do antiphospholipid antibodies enhance thromboembolic risk in patients with cancer?

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The association between thrombosis and cancer was first observed by Trousseau in 1865. Since then, numerous studies have shown that thromboembolism is a common complication of cancer, occurring in 15% of all cancer patients.\(^1\)\(^2\) Despite extensive research and modern interventions, thromboembolic disorders are still the major cause of morbidity and mortality in this population. The risk of thromboembolic events is 4-fold higher in patients with cancer than in the general population and this risk is further increased in patients undergoing chemotherapy.\(^2\)\(^3\) Much of this high risk is attributed to cancer itself. However, patient-related factors such as age, performance status, body mass index, underlying comorbidities, and therapy also represent considerable factors. The biological origin of thromboembolic events is related to the procoagulant, hypoxic, and inflammatory state associated with tumors, especially at advanced stages.\(^4\) Multiple mechanisms contribute to the hypercoagulable state observed in cancer, which leads to complex interactions among various factors, such as tissue factors, platelet and endothelial activation, coagulation abnormalities, procoagulants secreted by tumor cells, abnormal blood flow, and abnormal tumor angiogenesis.\(^1\)\(^4\) The question arises whether antiphospholipid antibodies (aPLs) additionally increase the thromboembolic risk in patients with malignant diseases.

Antiphospholipid antibodies constitute a heterogeneous group of autoantibodies directed against phospholipids or certain phospholipid-binding plasma proteins and their elevated levels in an individual are associated with a predisposition to thrombus formation.\(^5\) The occurrence of one or more clinical episodes of thrombosis and/or complications during pregnancy, such as miscarriage or preterm delivery, in conjunction with significant levels of aPLs including lupus anticoagulants (LAs), anticardiolipin antibodies (aCLs), and anti-β2-glycoprotein I antibodies (anti-β2GPIs) indicates the presence of antiphospholipid syndrome (APS).\(^7\) Antiphospholipid antibodies can be measured with 2 types of assays: LAs interfere with phospholipid-dependent coagulation tests in vitro, while other types of aPLs are measured with various immunosassays. Both LAs and aCLs can be directed against β2GPI or other antigenic targets such as prothrombin, protein C, protein S, tissue plasminogen activator, and annexin.\(^1\) The prevalence of elevated aPL levels has been reported in 1% to 5% of healthy young people, increasing by up to 50% in older patients with chronic diseases. The clinical significance of aPLs in healthy people remains elusive. Of note, not every test positive for aPLs is of clinical significance and patients with aPLs are at different levels of risk of adverse events associated with aPLs. Therefore, patients having aPLs together with other cardiovascular risk factors, such as high blood pressure, elevated cholesterol levels, diabetes, smoking status, or obesity, are at higher risk of adverse events. According to the current laboratory criteria for APS, aPLs should be present in tests performed twice at least 12 weeks apart.\(^7\)

The medium-to-high titers of aPLs are clinically more significant than lower levels, and double or triple positivity increases the risk of adverse events. A systematic review of observational studies excluding patients with autoimmune diseases reported a pooled prevalence rate of aPLs in up to 23.3% of patients with stroke, 23% with myocardial infarction, 15.8% with deep vein thrombosis, and 13% of women with adverse events during pregnancy.\(^6\)

A high prevalence of aCLs, anti-β2GPIs, LAs, antiphosphatidylincholine, antiphosphatidylserine, antiphosphatidylinositol, antiphosphatidylethanolamine, and antiprothrombin antibodies was observed in patients with various types of hematological malignancies and solid tumors.\(^2\) Therefore, an already increased risk of developing thrombosis in cancer patients is even higher in the aPL carriers. The reported prevalence of
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Elevated aPL levels in patients with cancer varies from less than 5%, which is the prevalence observed in healthy individuals, to up to 70%. This wide range is partly due to different methods, study designs, and inconsistent definitions of aPL positivity in the medical literature. In general, aPL assays are very heterogeneous and poorly standardized. In addition, most studies examined the prevalence of aPLs only once and did not repeat the test after 3 months, so the frequency may be overestimated. In a recent systematic review of observational studies, an increased risk of developing aPLs in patients with gastrointestinal, urogenital, and lung cancer was found to lead to thromboembolic events and death. In addition, a 17-year observational study of 1592 women free of thrombotic manifestations, with 3 consecutive spontaneous abortions before the 10th week of pregnancy or fetal death at or after the 10th week of pregnancy showed that the risk of cancer is significantly higher in women with a history of obstetric APS than in the general population.

In this issue of Polish Archives of Internal Medicine (Pol Arch Intern Med), Majdan et al investigated the presence of criteria and noncriteria aPLs in patients with uterine malignancies. There are 2 types of cancers that develop from the wall of the uterus: endometrial cancer develops from the lining of the uterus, and uterine sarcomas develop from the muscles or the supporting tissue of the uterus. In the study by Majdan et al., the authors did not distinguish between the 2 types of uterine cancers and compared 70 patients with uterine malignancies (UMs) with a group of 81 patients with noncancerous gynecological diseases (NCGDs). This study is of clinical value, as there are limited data on the occurrence of criteria and noncriteria aPLs in patients with malignant diseases of the female reproductive tract. The authors showed that noncriteria aPLs (against phosphatidic acid, phosphatidylserine, annexin V, and prothrombin) are more common in patients with UM than in those with NCGD. In contrast, the levels of criteria aPLs did not significantly differ between the UM and NCGD groups. Of note, several studies have linked noncriteria aPLs, especially anti–prothrombin antibodies, with obstetric complications, while they could not confirm the association with either anti–β2GPIs or LAs. It is possible that LAs and anti–β2GPIs are associated with thrombotic APS rather than obstetric APS, while aCLs and antibodies against phosphatidylserine–prothrombin complex appear to be related to both types of APS.

Several factors limited the study conducted by Majdan et al. First, it was conducted in a single center. Multicenter replication studies should be conducted to confirm their findings. Second, the 2 groups of patients compared in that study were not matched by age. In fact, the group with UM was significantly older than the NCGD group. It is known that the concentrations of aPLs increase with age. This raises the question whether age might have influenced the observed difference in aPL concentrations and whether this is exclusively due to the presence of solid tumors. Third, Majdan et al measured the levels of aPLs in the study population on only one occasion. Of note, aPLs might be transient during infections or in some other conditions. This is the main reason why the classification criteria for APS advise clinicians to repeat the test for aPLs after 12 weeks. A prospective study, in which healthy blood donors were tested for aPLs twice one year apart, showed a 10% positivity for aCLs and 1% positivity for LAs at the first measurement. Importantly, less than 1% of the study subjects were still positive after one year. Fourth, aPLs could be a noncausal artifact rather than a direct risk factor for thrombosis, especially since the authors could not find a direct correlation between aPLs and thrombosis. The risk of thrombosis is also strongly related to the type of surgical intervention—laparotomy or laparoscopy. Therefore, information on the type of surgical intervention and the incidence of thrombosis and aPL levels would be very informative.

In summary, the levels of aPLs seemed to be elevated in patients with different malignancies further increasing their risk of thromboembolic events. In the future, it would be valuable to conduct well-designed large-scale population studies as well as longitudinal studies of patients with various types of cancers to determine the actual risk and to confirm whether the increased prevalence of aPL positivity is of transient nature. Although the presence of aPLs can help to predict the thromboembolic risk, there are currently no meaningful data that would recommend aPL screening in patients with cancer.

ARTICLE INFORMATION

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REFERENCES


