

# ANTIPHOSPHOLIPID SYNDROME AND CANCER

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## Abstract

Antiphospholipid antibodies syndrome (APS) is an acquired prothrombotic status, that is due to the occurrence of a certain type of autoantibodies directed against negatively charged phospholipid structures – hence the name. Neoplasia is also characterized by a systemic procoagulant status, through various mechanisms. Obviously, both conditions may occur in the same patient, raising the question of a possible causal relation. Regardless of the potential liaison between the two events, clinicians caring for neoplastic patients as well as for APS patients, should be aware of the presence of both conditions in the same patient, as this has important therapeutic consequences.

**Keywords:** antiphospholipid syndrome, antiphospholipid antibodies, cancer

## INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease, characterized by a pro thrombotic status which is due to the presence of antiphospholipid antibodies (aPL). Classically and part of the Sydney consensus on diagnostic criteria, these antibodies are anti cardiolipin (aCL) antibodies IgG or IgM, anti-beta-2-glycoprotein-I ( $\alpha\beta 2$ GPI) antibodies IgG or IgM and lupus anticoagulant (LA). The first 2 are identified through enzyme-linked immunosorbent assays (ELISA), while the latter is identified through functional assay [1]. The clinical manifestations associated to APS pertain to vascular thrombosis and pregnancy morbidity. In order to make a correct diagnosis of APS, as per the Sydney criteria, one clinical and one laboratory criterion must be met [2]. It must be stressed out that the presence of aPL alone does not establish the diagnosis of APS; a clinical manifestation attributable to the afore mentioned antibodies, must also be present.

Noteworthy, interestingly enough, low levels of aPL may also be found in otherwise normal people. Actually, in around 1-5% of healthy young persons,

one can find aPL antibodies, with no known significance. This prevalence increases to 50% among elderly people that have a chronic disease [3]. Unfortunately, we do not know yet the importance and significance of these aPL antibodies in these people as we do not know what is the prevalence of APS in these groups of individuals. So, the presence of these kind of antibodies in these groups of people might be an epiphenomenon of some kind, or it might be the case that, in some particular circumstances, they "become" pathogenic and produce clinical manifestations in the form of APS. Nevertheless, the annual incidence of APS in the general positive for aPL population is 2.1 new cases per 100,000 persons and the estimated prevalence is 50 cases per 100,000 persons [4].

Some 1% of patients with APS, may present with a severe form of the disease, in which multiple organ failure is the main manifestation, known as catastrophic APS (CAPS) [5].

Antiphospholipid syndrome is classified, from an etiological point of view, as primary (when there is no evidence of any plausible etiology) and secondary. As secondary causes of APS, we recognize auto-

immune diseases (mostly systemic lupus erythematosus), neoplasia, use of certain medicines, infections and some other clinical situations [6].

## **CORRELATION BETWEEN ANTIPHOSPHOLIPID ANTIBODIES AND CANCER**

When it comes to cancer, it is well known that this condition, regardless of the type, is associated with a fourfold increase in thrombosis risk. Moreover, if the cancer is treated using chemotherapy, the risk of thrombosis increases even further: six-fold [7]. So, the higher risk is encountered in patients having advanced cancer, while receiving chemotherapy [8]. In addition, thrombosis may be the first manifestation of a malignancy: around 10% of patients with “idiopathic” thrombosis will be diagnosed as having a form of cancer in the next 5 to 10 years after the initial thrombotic episode [9]. Usually, recurring venous thrombosis in the context of cancer, also known as Trousseau’s syndrome, is difficult to treat [6].

The presence of aPL antibodies has been rather extensively reported in association with various solid and hematological cancers; this has led to the hypothesis that aPL might have a pathogenic role in the development of thrombosis in malignancies [10-12]. The mechanism by which aPLs are produced in cancer patients are poorly understood. The relation between cancer and the presence of antinuclear antibodies is known for quite a long time, suggesting the possibility of any other immunological abnormalities [13]. The aPL antibodies may be the consequence of the presence of the cancer or of the specific cancer therapy. Furthermore, since the appearance of cancer immune therapies, which now we know can have quite a stimulating effect on the immune system, one might expect the increase in occurrence of autoantibodies in patients treated with this kind of therapies [14-15]. There are many suggestions as to what are the mechanism underlying the production of aPL antibodies in cancer: 1. Secretion of aCL antibodies by the tumor cells; 2. Production of monoclonal immunoglobulins with LA and aCL activities; 3. Production of autoantibodies as a response to some tumor antigens [16]. Six years ago, it has been demonstrated that the aPL-positive IgG from patients with autoimmune disease rapidly accelerates tumor angiogenesis and, thus, tumor progression and extension [17]. It has also been shown that, in the circumstance of cancer, there is an activation of endothelial function with the expression of tissue factor, as well as an ac-

tivation of platelets. All of these, disrupt the coagulation and fibrinolysis pathways, leading to the hypercoagulation status associated with neoplasia [18,19]. It is noteworthy that, in the presence of aPS, the same mechanisms contribute to the development of thrombosis characteristic of APS [20]. In addition to all of these mechanism, there seem to exist some genetic links between thrombosis development and APS and cancer [21,22]. So, probably in the future, studies dedicated to all of these hypothesis may reveal some new insights into the intimate mechanisms of occurrence of thrombosis in aPL positive cancer patients, as well as into some new therapeutic options for treating this potentially life-threatening clinical picture.

## **MALIGNANCIES AND ANTIPHOSPHOLIPID SYNDROME**

As to the interrelation APS-cancer, there can be, at least theoretically, two ways of looking at it: the presence of aPL antibodies in cancer and the presence of cancer in aPL positive patients.

There are numerous reports and studies pertaining to the occurrence of aPLs in cancer. The prevalence and the incidence of these antibodies variable depending on the study, but nevertheless, their presence should be accounted for in order to be aware of a supplementary thrombotic risk in neoplastic patients. Bazan et al. reported in their study a prevalence of 24% of aPLs, which was significantly higher than that of controls ( $p < 0.0001$ ). If there were to separate on types of aPL, 5.8% were LA, 12.14% were aCL and 5.8% were of the anti- $\beta_2$ -GPI type. Interestingly and remarkable is the fact that thrombotic events did not differ significantly in occurrence, between the aPL positive and negative patients, respectively [23]. In concordance with these findings, an Iranian group reported in 156 cancer patients (67% with a solid cancer, the rest with a hematological cancer) a prevalence of 21.2% of aPLs, with no significant difference between the two types of cancer [24]. In 2006, Miesbach et al. reported on 58 patients with solid cancers (77%) and hematologic cancers (33%). They found that aCL antibodies were positive in 48% of solid tumor patients and 62% of hematologic cancers, while LA was positive in 54% of the solid tumor patients and 42% of hematologic cancer patients [25]. In non-Hodgkin’s lymphoma, the prevalence of high levels of aPLs is 41%, the most prevalent serotype being the anti- $\beta_2$ -GPI antibodies (86 patients) [26]. In Romania, Tanaseanu et al. reported in 2001,

confirmed APS in 18 of 46 patients with cancer, 14 being LA positive and 3 aCL positive [27].

The other side of the aPL-cancer interrelation, is the occurrence of cancer in patients with antiphospholipid antibodies. In this respect, already in 1988, Jude and co-workers, analyzing patients with LA-positive autoimmune diseases, revealed the presence of any form of cancer, in 17% of them [28]. In another study [29], 6 years later-on, the prevalence of cancer among aPLs patients, was 20%. Moreover, from another study, with a follow-up period of 4 years, among 360 aPL-positive patients, four developed non-Hodgkin's lymphoma (this incidence being significantly higher than in the general population. The authors postulate that patients presenting APS are at increased risk of developing malignancies [30]. Surprisingly, this finding was confirmed by the observation that 41.6% of aPL-positive patients developed a type of solid malignancy [10]. Nine percent of CPAS registry patients, developed cancer, with hematologic cancer (leukemia and lymphoma) being the most prevalent [31]. Between 1998 and 2018, there were 38 case-reports of associated cancer to APS [11]. Since "post hoc, ergo propter hoc" is not always true, it would be very interesting to try and solve this peculiar and somewhat unexpected occurrence of neoplasia in patients displaying laboratory and/or clinical signs of APS. Of course, it may be that those events are just two causally unrelated events,

one being just "the innocent bystander" of the other, or the other way around with aPLs really being causative of neoplasia. It is a relation that has not been fully explored or understood and, when it will be so, it might seriously impact the management of APS in context of cancer and vice-versa.

As it has already been described for some time, there is a special type of APS, called the seronegative APS, in which patients have typical clinical manifestation intensely suggestive of APS, but in the persistent absence of aPLs (conventional ones) on multiple occasions [32]. There are some reports of malignancies observed in such patients, namely seronegative APS patients [33,34], but of course it is very difficult to ascertain these occurrences as causative not random, in nature.

## CONCLUSIONS

To conclude, even though aPL positivity may help in predicting risk of thrombosis in cancer patients, there is not enough evidence that determining aPLs should become routine practice in every neoplasia patient. On the other hand, there is quite a body of evidence that cancers are associated with an increased risk of developing aPL antibodies and clinicians caring for neoplastic patients should be aware of this increased risk, which adds on to the "intrinsic" thrombotic risk of such a fragile patient.

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