



Antiphospholipid antibodies and malignancies

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ABSTRACT

Since the 1980s it is known that an important thrombogenic mechanism is mediated by antiphospholipid antibodies (aPL). Aim of this review is to discuss how much aPL presence may worsen the thrombophilic state of neoplastic patients and how much cancer may worsen and extend the thrombophilic state of patients with Antiphospholipid Syndrome (APS).

In the last years a higher prevalence of aPL was observed in patients with solid tumors compared to controls. These patients, already at higher risk of thrombosis, may have a still higher risk when aPL carriers. Those with a solid malignancy seem to be more likely to have a thrombotic event compared to patients with a hematological disorder. On the other hand aPL presence may be a risk factor for malignancies (particularly hematological).

Even if the significance of aPL and cancer relationship has to be further investigated, clinicians should remember that in neoplastic patients aPL presence can increase thromboembolic risk and in healthy carriers can increase the possibility of developing a malignancy.

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1. Introduction

Thrombosis can be the first manifestation of cancer and about 10% of patients with idiopathic thrombosis may be diagnosed with subsequent cancers over the next 5–10 years [1]. This association is well known since the nineteenth century when Trousseau described the presence of thrombophlebitis migrans in neoplastic patients.

Patients with cancer are at higher risk of thromboembolic complications than healthy people for many reasons. First there is a complex relationship between cancer and host cells that troubles the balance between coagulation and fibrinolysis [2]. Tumor needs of new blood vessels to grow, but proangiogenic factors as vascular endothelial growth factor can also promote a thrombophilic state by causing the secretion of procoagulant substances from endothelial

cells. The same tumor cells can secrete procoagulants [3] and inhibit anticoagulant properties of endothelial cells; the tumor can induce stasis also by local vascular invasion [4]. Cancer takes advantage from a thrombophilic state because essential factors of haemostasis like tissue factor, thrombin, urokinase plasminogen activators can promote its growth and progression [5]. Finally general responses of the host to the tumor [6], prolonged immobilization, use of central venous catheters and cytotoxic therapy participate in thrombophilic state of these patients [4].

Since the 1980s it is known that another important thrombogenic mechanism is mediated by antiphospholipid antibodies (aPL). The association between aPL and thrombotic events initially came from clinical observations [7], but was also confirmed in animal models [8] and in prospective studies [1]. In fact aPL injection in healthy animals induces fetal loss, but also increases the formation speed of the thrombus, its size and its disappearance time. Prospective studies on humans highlighted how the presence of aPL in patients with a previous thrombotic event or obstetric failure increases the risk of relapse

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[9]. Over time has become clear that in young patients, in which traditional risk factors are less frequently represented, aPL are one of the most important risk factors for arterial and venous thrombosis, stroke and myocardial infarction. All these observations together led to the definition of a new syndrome, the antiphospholipid syndrome (APS) [10], who represents an acquired thrombophilic condition.

How much aPL presence may worsen the thrombophilic state of neoplastic patients and how much cancer may worsen and extend the thrombophilic state of APS patients will be discussed in these pages.

2. Antiphospholipid antibodies in patients with malignancies

In the last years a higher prevalence of aPL was observed in patients with solid tumors compared to controls [11]. This pattern was also observed in patients with hematological malignancies [12]. As recently described [13] this association was reported for a large variety of malignancies. The reasons of this antibody increased production are only partially clarified: their production may be induced by particular immunotherapy of cancer such as interferon α [14] or started by immune system response to new tumor antigens [15]. In particular it is possible that autoantibodies to malignant cells arise secondary to changes in the cell membrane that induce exposure of certain antigens that are normally facing the intracellular compartment [13]. This is the case of phosphatidylserine, which is exposed on the outer membrane of cells undergoing apoptosis. The exposure of this lipid directly triggers coagulation cascade by providing a procoagulatory surface [16], allows the binding of circulating Beta2-Glycoprotein I (B2GPI) and subsequently of aPL leading to clot formation [6]. It is also possible that tumoral cells directly synthesize antibodies as in the case of Multiple Myeloma or Waldenstrom's Macroglobulinemia. We cite as an example the IgM lambda type paraprotein directed against phospholipids used to describe the mechanism of lupus anticoagulant [17]. Anyway in the case of paraproteins, antibody monoclonal nature gives a particular specificity to aPL that, if different from that observed in classic APS, could be insignificant for thrombogenesis.

It is reasonable to think that patients with malignancies, already at higher risk of thrombosis, may have a still higher risk when aPL carriers. It has been suggested that aPL, also reported in asymptomatic subjects, are not able alone to cause thrombosis and become pathogenetic when a second factor is present ("Two hits hypothesis"). In this context, in a subject with aPL, the cancer could be the second hit that triggers thrombosis. In fact, according to this hypothesis, different authors reported a significantly higher rate of thromboembolic events in aPL positive cancer patients compared to controls, considered as subjects with the same malignancy without aPL [11,12]. Some authors noted that patients with a solid malignancy are much more likely to have a thrombotic event compared to patients with a hematological disorder [18]. So, even if high levels of aPL are frequent in hematological malignancy, a clinical manifestation would be more rare.

These antibodies can be responsible of various manifestations in neoplastic patients. Most authors agree that in patients with cancer, as in the classic APS, thrombotic events are mainly venous, in particular deep venous thrombosis and pulmonary embolism [6,13], even if one study reported that most patients with solid malignancies suffered from arterial thrombosis, in particular from strokes [18]. Other rare manifestations related to aPL, described in patients with cancer, include necrotizing leg ulcers, nonbacterial thrombotic endocarditis, recurrent stent thrombosis and transverse myelitis [5]. Recently two cases of severe hand digital ischemia have been reported in patients with aPL. This unusual form of Raynaud's phenomenon was in both cases the presenting symptom of metastatic solid tumors [19].

Even if the above observations show that aPL presence in patients with cancer promotes thrombosis, it is necessary to remember that, after a consistent follow-up, also patients with a malignancy and aPL without events are reported [20,21].

These data, apparently discordant, merit two brief considerations: A) the presence of aPL without clinical manifestations in patients with cancer has been prevalently reported in hematological disorders, while in solid tumors the association seems more constant; B) the so called aPL are a polyclonal family of antibodies, among which only a few is thrombophilic. Some authors suggested that only certain isotypes, like IgG or IgA, tend to persist and to be associated with thrombotic events. Otherwise transient IgM would not be pathological [6,22,23]. Another recent hypothesis (today the most accredited in patients with autoimmune diseases) is that antibodies associated with thrombosis are those that recognize the domain I of B2GPI [24]. In fact, also in neoplastic patients aPL could have different specificity more or less related to thrombogenic tendency.

3. Malignancies in patients with antiphospholipid antibodies

Studying natural history of aPL healthy carriers, Finazzi et-al. [25] reported that, after a median follow-up of 3.9 years, surprisingly hematological malignancies were a major cause of morbidity and mortality. In particular non-Hodgkin's lymphoma incidence was significantly higher than the expected one in general population. The authors concluded that aPL presence may be a risk factor for hematological malignancies and the possibility of these diseases should be born in mind in the initial evaluation and during the follow-up of these patients. This finding was recently supported by Gomez-Puerta et-al. [26] who observed that 26% of patients with aPL and malignancies suffered from a hematological cancer. Also Endler et-al. [27] found in a large cohort of patients with positive anticardiolipin antibodies that the risk of cancer-related mortality was increased 2.6-fold. A prospective study conducted during 5 years on 1,000 APS patients by Cervera et-al. [28] confirmed that malignancies are one of the most frequent causes of death in these patients.

On the other hand it was reported that aPL were dramatically reduced or disappeared after underlying malignancy remission, while they were persistent in those patients who did not respond to the treatment [5].

According to the classification criteria [10] a patient with one or more episodes of vascular thrombosis and persistent positive aPL is affected by APS. But additional risk factors for thrombosis should be assessed and patients should be stratified according to their presence or absence. In this context, particularly in elderly patients, malignancies can be one of these additional factors.

One of the most severe complications of aPL presence is the Catastrophic Antiphospholipid Syndrome (CAPS) [29]. This is a serious condition characterised by the rapid chronological development of fulminant thrombotic complications that predominantly affect small vessels with multiple organ failure and frequent death of the patient. Since 2000 CAPS cases, fortunately rare, are collected in an international registry on the web, promoted by the European Forum on Antiphospholipid Antibodies. The registry reported a documented associated cancer in 9% of all included patients [30]. In most patients malignancy was noted as the precipitating factor for CAPS. Among CAPS associated cancers lymphomas and leukemias are the most representative group. As reported above, aPL presence in hematological malignancy do not necessary enhance the risk of large vessel thrombosis. In fact the association between CAPS and these malignancies underline how in this severe syndrome the prevalent pathogenetic mechanism is small vessel thrombosis. Nevertheless the prognosis is poor when these two conditions (CAPS and cancer) are combined.

4. Conclusions

Even if the significance of aPL in patients with malignancy and the risk of malignancy in aPL positive patients have to be further investigated, some considerations appear useful for clinical practice: A) in some *neoplastic patients* aPL presence seems to be associated to a

higher risk of thromboembolic events. In these cases low molecular weight heparin prophylaxis should be considered. During the follow-up aPL reduction might help to confirm remission; B) in the initial evaluation and during the follow-up of aPL healthy carriers the possibility of developing a malignancy (especially hematological) should be born in mind; C) in elderly patients with thrombosis and high aPL titles without evident causes (primary APS) an underlying malignancy should be excluded; D) in case of a serious ischemic aPL associated event or a CAPS a malignancy should be considered as the precipitating factor.

Take-home messages

- In neoplastic patients aPL can be associated to a higher risk of thromboembolic events;
- aPL healthy carriers can be at higher risk to develop a malignancy;
- In case of serious ischemic aPL associated event, CAPS or primary APS, especially in elderly patients, a malignancy should be excluded.

References

- [1] Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. Duration of Anticoagulation Trial. *N Engl J Med* 2000;342(26):1953–8.
- [2] Dogan M, Demirkazik A. Venous thromboembolism in patients with cancer and its relationship to the coagulation cascade and vascular endothelial growth factor. *Support Cancer Ther* 2005;3(1):28–34.
- [3] Lip GYH, Chin BSP, Blann AD. Cancer and the prothrombotic state. *Lancet Oncol* 2002;3(1):27–34.
- [4] Falanga A, Rickles FR. Pathophysiology of the thrombophilic state in the cancer patient. *Semin Thromb Hemost* 1999;25(2):173–82.
- [5] Pham C, Shen Y. Antiphospholipid antibodies and malignancy. *Hematol Oncol Clin North Am* 2008;22(1):121–30.
- [6] Battistelli S, Stefanoni M, Petrioli R, Genovese A, Dell'Avanzato R, Donati G, et al. Antiphospholipid antibodies and acute-phase response in non-metastatic colorectal cancer patients. *Int J Biol Markers* 2008;23(1):31–5.
- [7] Tincani A, Meroni PL, Brucato A, Zanussi C, Allegrì F, Mantelli P, et al. Antiphospholipid and anti-mitochondrial type M5 antibodies in systemic lupus erythematosus. *Clin Exp Rheumatol* 1985;3(4):321–6.
- [8] Pierangeli SS, Liu XW, Barker JH, Anderson G, Harris EN. Induction of thrombosis in a mouse model by IgG, IgM and IgA immunoglobulins from patients with the antiphospholipid syndrome. *Thromb Haemost* 1995;74(5):1361–7.
- [9] Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;346(10):752–63.
- [10] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4(2):295–306.
- [11] Zuckerman E, Toubi E, Golan TD, Rosenvald-Zuckerman T, Sabo E, Shmuel Z, et al. Increased thromboembolic incidence in anti-cardiolipin-positive patients with malignancy. *Br J Cancer* 1995;72(2):447–51.
- [12] Pusterla S, Previtali S, Marziali S, Cortelazzo S, Rossi A, Barbui T, et al. Antiphospholipid antibodies in lymphoma: prevalence and clinical significance. *Hematol J* 2004;5(4):341–6.
- [13] Reinstein E, Shoenfeld Y. Antiphospholipid syndrome and cancer. *Clin Rev Allergy Immunol* 2007;32(2):184–7.
- [14] Becker JC, Winkler B, Klingert S, Bröcker EB. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. *Cancer* 1994;73(6):1621–4.
- [15] Sawamura M, Yamaguchi S, Murakami H, Amagai H, Matsushima T, Tamura J, et al. Multiple autoantibody production in a patient with splenic lymphoma. *Ann Hematol* 1994;68(5):251–4.
- [16] Vogt E, Ng AK, Rote NS. Antiphosphatidylserine antibody removes annexin-V and facilitates the binding of prothrombin at the surface of a choriocarcinoma model of trophoblast differentiation. *Am J Obstet Gynecol* 1997;177(4):964–72.
- [17] Thiagarajan P, Shapiro SS, De Marco L. Monoclonal immunoglobulin M lambda coagulation inhibitor with phospholipid specificity. Mechanism of a lupus anticoagulant. *J Clin Invest* 1980;66(3):397–405.
- [18] Miesbach W, Scharrer I, Asherson R. Thrombotic manifestations of the antiphospholipid syndrome in patients with malignancies. *Clin Rheumatol* 2006;25(6):840–4.
- [19] Grossman A, Gafter-Gvili A, Green H, Ben Aharon I, Stemmer SM, Molad Y, et al. Severe digital ischemia – a presenting symptom of malignancy-associated antiphospholipid syndrome. *Lupus* 2008;17(3):206–9.
- [20] Genvresse I, Lüftner D, Späth-Schwalbe E, Buttgerit F. Prevalence and clinical significance of anticardiolipin and anti-beta2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma. *Eur J Haematol* 2002;68(2):84–90.
- [21] Miesbach W, Scharrer I, Asherson RA. High titres of IgM-antiphospholipid antibodies are unrelated to pathogenicity in patients with non-Hodgkin's lymphoma. *Clin Rheumatol* 2007;26(1):95–7.
- [22] Yoon KH, Wong A, Shakespeare T, Sivalingam P. High prevalence of antiphospholipid antibodies in Asian cancer patients with thrombosis. *Lupus* 2003;12(2):112–6.
- [23] de Meis E, Monteiro RQ, Levy RA. Lung adenocarcinoma and antiphospholipid antibodies. *Autoimmun Rev* 2009 [Electronic publication ahead of print].
- [24] de Laat B, Wu X, van Lummel M, Derksen RHW, de Groot PG, Rand JH. Correlation between antiphospholipid antibodies that recognize domain I of beta2-glycoprotein I and a reduction in the anticoagulant activity of annexin A5. *Blood* 2007;109(4):1490–4.
- [25] Finazzi G. The Italian registry of antiphospholipid antibodies. *Haematologica* 1997;82(1):101–5.
- [26] Gómez-Puerta JA, Cervera R, Espinosa G, Aguiló S, Bucciarelli S, Ramos-Casals M, et al. Antiphospholipid antibodies associated with malignancies: clinical and pathological characteristics of 120 patients. *Semin Arthritis Rheum* 2006;35(5):322–32.
- [27] Endler G, Marsik C, Jilma B, Schickbauer T, Vormittag R, Wagner O, et al. Anticardiolipin antibodies and overall survival in a large cohort: preliminary report. *Clin Chem* 2006;52(6):1040–4.
- [28] Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Kiss E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicenter prospective study of 1,000 patients. *Ann Rheum Dis* 2008 [Electronic publication ahead of print].
- [29] Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. *Medicine* 1998;77(3):195–207.
- [30] Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, Gomez Puerta J, Bucciarelli S, et al. The catastrophic antiphospholipid (Asherson's) syndrome and malignancies. *Autoimmun Rev* 2006;6(2):94–7.

Regression of systemic lupus erythematosus after development of an acquired toll-like receptor signaling defect and antibody deficiency

Toll-like receptor 9 (TLR-9) and TLR-7 may have a role in the production of anti-DNA and anti-RNA autoantibodies, respectively, but murine models do not clearly demonstrate their contribution to the development of systemic lupus erythematosus (SLE). Herein, **Visentini M. et al. (Arthritis Rheum 2009; 60: 2767–71)** describe a patient with SLE who had long-lasting remission of her autoimmune disease after development of an antibody deficiency resembling common variable immunodeficiency (CVID). After CVID had developed, anti-dsDNA antibodies disappeared, although antinuclear antibodies remained positive for > 10 years. In vitro studies revealed that the patient's B cells proliferated poorly and failed to differentiate into plasmablasts after stimulation of either TLR-9 or TLR-7, providing evidence for an acquired defect of the signaling pathway downstream of these TLRs. These observations suggest, although indirectly, that signaling through TLR-9 and TLR-7 is important in the pathogenesis of human SLE, and indicate that investigation of potential treatment strategies with TLR antagonists is warranted.

Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus

Studies have suggested involvement of interleukin 17 (IL-17) in autoimmune diseases, although its effect on B cell biology has not been clearly established. Here, Doreau A. et al. (*Nat Immunol* 2009; 10: 778–85) demonstrate that IL-17 alone or in combination with B cell-activating factor controlled the survival and proliferation of human B cells and their differentiation into immunoglobulin-secreting cells. This effect was mediated mainly through the nuclear factor-kappaB-regulated transcription factor Twist-1. In support of the relevance of these observations and the potential of involvement of IL-17 in B cell biology, the authors found that the serum of patients with systemic lupus erythematosus (SLE) had higher concentrations of IL-17 than the serum of healthy people and that IL-17 abundance correlated with the disease severity of SLE.