Malignancies: A Possible "First Hit" in the Development of Catastrophic Antiphospholipid Syndrome?

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KEY WORDS: catastrophic antiphospholipid syndrome (CAPS), Asherson's syndrome, antiphospholipid syndrome (APS), neoplasia, thrombotic microangiopathy

IMAJ 2014; 16: 583–584

In their intriguing study reported in this issue of *IMAJ*, de Meis et al. [1] introduce the complicated relationship between the immune and coagulation systems, suggesting that autoimmunity may be generated in the context of an antineoplastic immune phenomenon, especially when a pro-coagulant factor occurs at the same time. Moreover, they underline the particularly severe prognosis of a subgroup of patients in whom a catastrophic antiphospholipid syndrome complicates a neoplastic condition.

CAPS, or Asherson's Syndrome, is a life-threatening condition resulting from rapidly progressive widespread thromboses mainly affecting the microvasculature in the presence of antiphospholipid antibodies [2]. Within a few days, the patient develops multiorgan failure with pulmonary distress, renal failure with severe hypertension, and cerebral, cardiac, digestive or cutaneous involvement. CAPS develops in fewer than 1% of patients with antiphospholipid syndrome [3]. The characteristics of CAPS were redefined in 2003 [4] by a set of classification criteria that include:

- evidence of the involvement of three or more organs, systems and/or tissue
- development of the clinical manifestations simultaneously or in less than a week
- confirmation by histopathology of small vessel occlusion in at least one organ or tissue
- laboratory confirmation of the presence of antiphospholipid antibodies.

The third criterion reflects the key mechanism of the pathophysiology of CAPS that differentiates this variant from the classic antiphospholipid syndrome: in APS we usually observe thrombosis in a large vessel with only one area involved at a time, while in CAPS occlusion occurs at the same time in multiple vessels at the microvascular level. Kitchens et al. [5] have suggested that microvascular occlusions are themselves responsible for the ongoing thrombosis: clots continue to generate thrombin, fibrinolysis is depressed by an increase in plasminogen activator type-1, while the natural anticoagulant proteins such as protein C and thrombin are consumed.

Pro-inflammatory cytokines, several products of the activated complement system, and aPL themselves are able to activate endothelial cells and up-regulate adhesion molecules and tissue factor. At the same time, they act on leukocytes and platelets, increase their adhesion capacity and promote the local release of toxic mediators such as proteases and oxygen-derived free radicals. These multiple small vessel occlusions create a framework of thrombotic microangiopathy, which is responsible for multiple organ dysfunction and failure and causes extensive tissue necrosis, resulting in a systemic inflammatory response with excessive cytokine release from affected necrotic tissues [6,7].

Thrombotic microangiopathy and SIRS are responsible for the severe multiple manifestations of CAPS. The most frequently involved site is the abdomen, with renal disease in 71% of cases; pulmonary complications are next in frequency (64%), mainly acute respiratory distress and pulmonary embolism [8]. The involvement of the central nervous system (infarcts, encephalopathy), heart (valvular defects, myocardial dysfunction), and skin (livedo reticularis, purpura, necrosis) is also common.

Notably, CAPS occurs in 46% of patients with a previous diagnosis of APS, and in 53% of all patients there is a precipitating factor. In general, aPL-related clinical events respond to the so-called two-hit theory: a "second hit," a trigger event of any origin, is needed to activate the prothrombotic properties of aPL ("first hit") [9,10]. In CAPS the most frequently recognized trigger is infection, while cancer accounts for 5% of cases [6].

The complex relationship between aPL and neoplasia has already been investigated: patients with solid tumors or hematological malignancies have a higher prevalence of aPL. Malignant cells often develop modifications in their membrane, inducing the exposure of certain antigens that are normally located in the intracellular compartment, representing a possible target for autoantibodies [11]. There is also evidence supporting the role

CAPS = catastrophic antiphospholipid syndrome
APS = antiphospholipid syndrome
aPL = antiphospholipid antibodies
SIRS = systemic inflammatory response

of a specific immunotherapy for cancer (such as interferon-alpha) and for the direct synthesis of aPL by tumoral cells in hematological malignancies. Interestingly, some authors found that even if high levels of aPL are more frequent in hematological malignancies, a clinical thrombosis is more likely in patients with solid tumors [12].

Regarding prognosis, it is important to underline that CAPS, a severe condition, could be even more severe when associated with cancer. Miesbach and co-authors [13] compared CAPS patients with and without malignancies (based on 262 patients recorded in the CAPS registry until February 2006) and found similar clinical manifestations in the two groups, but 39% of neoplastic patients recovered as compared to 58% in the other group.

In conclusion, the rapid appearance of multiple thrombotic complications at the microvascular level in cancer patients should lead clinicians to consider the diagnosis of CAPS and subsequently initiate, as soon as possible, an "aggressive" treatment that includes glucorticoids as first-line therapy in addition to anticoagulation with heparin.

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