Catastrophic Antiphospholipid Syndrome in Cancer Patients: An Interaction of Clotting, Autoimmunity and Tumor Growth?

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ABSTRACT: Thrombosis is a common phenomenon in patients with malignancies. It is believed that thrombosis is multifactorial and that in addition to mechanisms directly associated with cancer and its treatment, it may also be related to the interaction between the immune system and clotting. The present work describes four cancer patients (three adults and one child) whose clinical course was characteristic of catastrophic antiphospholipid syndrome (CAPS) in intensive care units of the National Cancer Institute of Rio de Janeiro. The presence of findings similar to those in CAPS can be attributed to an unbalanced interaction between the immune system and coagulation.

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Thrombosis is a frequent complication in patients with cancer and is responsible for one in every seven deaths among cancer patients [1-4]. There is already evidence that the increased clotting activity – both clinical and laboratory – in cancer patients is responsible for the thrombotic events and also plays a role in neo-angiogenesis, a phenomenon essential for tumor growth [1,4,5]. This neo-angiogenesis explains why patients with thrombotic events have a worse prognosis (shorter survival) than those with the same type of cancer but without thrombosis [4,5].

Many recent studies have attempted to elucidate the role of coagulation activation in patients with thrombosis, but several questions have yet to be answered. Does the incidence of thrombosis vary according to the type of neoplasia? We already know that thrombosis is a multifactorial phenomenon, but is there a specific factor that triggers the event? Is there a tightly balanced interaction between the immune system and the process of coagulation, and if an imbalance occurs, does this lead to the thrombotic events common in cancer and inflammation? Is there a marker for this imbalance?

Several authors have shown that antiphospholipid antibodies can be detected in the peripheral blood of patients with malignancies, especially lymphoproliferative disorders (non-Hodgkin lymphomas and Hodgkin's disease) and lung adenocarcinoma [6,7]. However, whether or not these would be pathogenic antiphospholipid antibodies (i.e., with the ability to induce thrombosis) is not known. A study by our group demonstrated that lupus anticoagulant is a risk factor for the occurrence of thrombosis in patients with lung adenocarcinoma [3]. Associated with these findings, several reports showed that cancer is a risk factor for the development of catastrophic antiphospholipid syndrome [8,9]. CAPS is an acute and complex variant of the antiphospholipid syndrome. Its diagnosis is based on international criteria [10] [Table 1].

In this article we describe four events similar to CAPS in cancer patients (three adults and one child) and discuss the role of antiphospholipid thrombosis in cancer patients.

PATIENT DESCRIPTIONS

PATIENT 1

This patient was a 74 year old woman previously treated with surgery, radiotherapy and chemotherapy for breast cancer. Years later she developed colon/rectum adenocarcinoma that was treated surgically and on the 12th postoperative day she developed aspiration pneumonitis. She was admitted to the intensive care unit with respiratory insufficiency and norephinephrine dependence. After 24 hours the norepinephrine was discontinued but she still required pulmonary assistance (despite chest radiography showing improvement). Twenty-four hours later the patient developed ischemia in both hands and feet [Figure 1A], progressive reduction in urinary flow rate and increased serum creatinine. She was still taking antibiotics and at that stage there were no signs of infection, but she still required ventilator support.

Doppler ultrasound of the lower limbs showed venous and arterial thrombosis and echocardiography showed maran-

CAPS = catastrophic antiphospholipid syndrome

Table 1. Diagnostic criteria for catastrophic antiphospholipid syndrome (CAPS)

1. Evidence of involvement of three organs, systems, and/or tissues
2. Development of simultaneous manifestations in less than 1 week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
4. Laboratory confirmation of the presence of aPL (LAC and/or aCL and/or anti-2GPI antibodies)
Definite CAPS
All 4 criteria
Probable CAPS
• All four criteria, except for the involvement of only two organs, system, and/or tissues
• All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart related to the early death of a patient never tested for aPL before onset of CAPS
• 1, 2 and 4
• 1, 3 and 4, and the development of a third event in > 1 week but < 1 month, despite anticoagulation treatment

tic endocarditis. No other irregular antibodies apart from antiphospholipid antibodies were detected. Laboratory findings are presented in Table 2.

The treatment regimen included antibiotics, methylprednisolone pulse therapy, plasmapheresis and anticoagulation with enoxaparin. During anticoagulation the level of hematocrit fell and the anticoagulants were discontinued, but plasmapheresis was maintained. Her condition gradually improved, with total reperfusion of the hands and partial reperfusion of the legs; she no longer required respiratory and circulatory support and urinary output returned to normal. She was discharged from the ICU.

PATIENT 2

A 65 year old man with cholangiocarcinoma (histology: adenocarcinoma) underwent gastroduodenal pancreatectomy. Infectious peritonitis developed in the early postoperative period. On day 7 an examination of the abdominal cavity demonstrated diffuse bleeding in the peritoneum without specific focus. This was followed by septicemia and progressive increase in the output material of abdominal drains. A subsequent examination identified leakage from one of the jejunopancreatic anastomoses. Two days later the patient was reassessed according to the criteria described in Table 1. Laboratory tests indicated lupus anticoagulant antibody positivity [Table 2].

The patient did not experience a significant hypotension event but developed acute renal insufficiency failure that required mechanical ventilation. During surgery the following day for peritoneal bleeding, ischemic foci in the liver were verified. An antifibrinolytic agent was begun according to ICU routine. Since the bleeding continued at the site of laparoscopy, surgery was again performed, this time using plasma cryoprecipitate (fibrinogen 70 mg/dl) and platelets (platelet 55,000/mm^3). The patient continued to bleed. Plasmapheresis was started following the finding of positive lupus coagulant and organ ischemia. The inflammatory parameters worsened and 3 days later he was submitted for further surgery which identified extensive entero-mesenteric infarction, precluding the operation.

Material obtained during the last surgical procedure showed complete necrosis of the entire parenchymal liver tissue and a segment of the small intestine showing continuity with areas of inflammation, fibrin deposition, vascular and connective

ICU = intensive care unit

Table 2. Laboratory findings

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Lupus anticoagulant	Positive	Positive	Positive	Positive
Anticardiolipin IgG (U/ml)	1.6		NR	2.8
Anticardiolipin IgM (U/ml)	0.4		NR	1.4
Creatinine (normal up to 1.3)	1.0		1.3	2.3
Troponin (ng/dl) (High risk > 100 ng/dl)	NR	NR	50	852
Total CPK (U/L) (normal up to 190)	NR	NR	386	870
CPK MB (U/L) (normal up to 25)	NR	NR	33	315
C-reactive protein (normal < 0.5)	8.35		13.93	11.9
Antithrombin (%) (normal > 80)	95	19	87	47
Protein C (%) (normal > 70)	88.7	31.4	73.7	20.2
Platelets/mm^3 (normal 140,000–350,000)	179,000	55,000	236,000	32,000
PT (INR)	1.2	1.31	1.21	
aPTT	1.30	1.02	2.76	2.60
D-dimer (mg/dl) (normal < 0.5)	1.58	35.2	4.12	Higher than limits of equipment
Fibrinogen (normal >150)	NR	70	398	52
Ferritin (ng/ml)	117	206,655	3146	2875
Factor V (%) (normal > 70)	NR	64	NR	125
Factor IX (%) (normal > 70)	NR	106	NR	60
Factor X (%) (normal > 70)	NR	53	NR	86
Factor VII (%) (normal > 70)	NR	47	NR	79

Ig = immunoglobulin, CPK = creatine phosphokinase, CPK MB = MB isoenzyme of creatine kinase, PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time

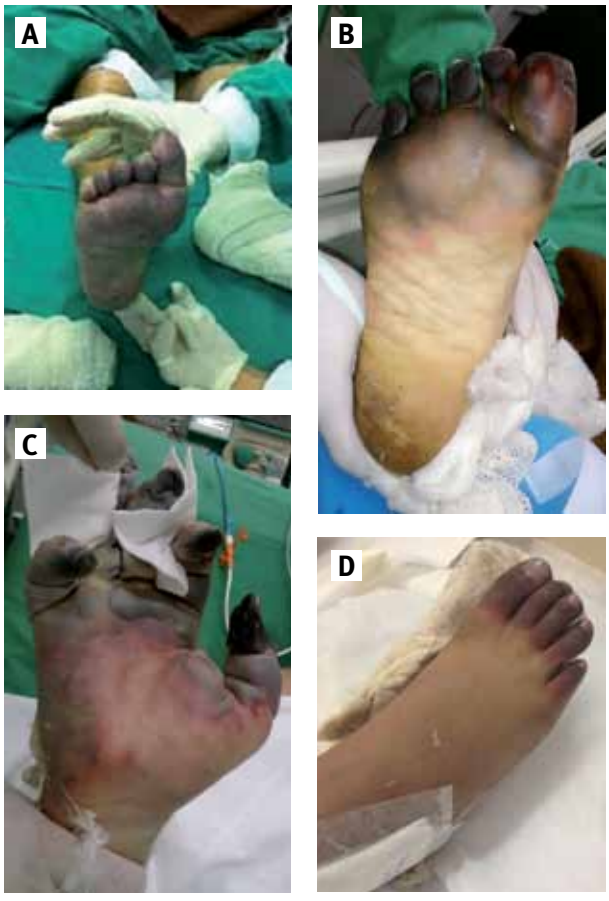
tissue proliferation, as well as congestion of blood vessels. The patient died less than 24 hours after surgery.

PATIENT 3

This patient was a 62 year old man with lung adenocarcinoma who was treated both surgically and with chemotherapy. During an infectious event lasting 72 hours he developed jugular vein thrombosis, peripheral arterial thrombosis (hands and feet), renal insufficiency (managed with dialysis) and circulatory failure (treated with a moderate dose of amine). The laboratory findings are listed in Table 2. No other irregular antibodies were detected.

Skin biopsies from the hands showed epidermis with segmental necrosis associated with hyaline thrombi in dermal vessels suggestive of thrombotic vasculopathy [Figure 1B and 1C]. The treatment included methylprednisolone pulse, plasmapheresis and anticoagulation with enoxaparin (following anti-Xa activity). The drainage fluid from the stomach indicated liquid stasis initially followed by stasis with blood later on. He died despite the treatment.

Figure 1. Arterial thrombosis in **[A]** patient 1, **[B]** patient 3, **[C]** patient 3, **[D]** patient 4



PATIENT 4

This patient was a child, 9 years old, male, diagnosed with Ewing's sarcoma of the right fibula. In the immediate postoperative period, following distal fibulectomia, he developed a high fever associated with episodes of disorientation and hemodynamic instability. Forty-eight hours after the surgery the patient developed arterial thrombosis mainly in the lower limbs [Figure 1D], myocardial ischemic injury with elevated cardiac enzymes, and acute renal failure requiring dialysis. Blood cultures from the catheter insertion revealed *Klebsiella pneumoniae*, and the device was removed. Serial measurements showed lupus anticoagulant-positive serum [Table 2].

The patient was treated with monoclonal immunoglobulin, plasmapheresis and anticoagulation with low molecular weight heparin. During treatment, there was a significant improvement in hemodynamic status and renal function and total reperfusion of ischemic lower limbs. He was discharged 50 days after admission, with full anticoagulation and able to continue his cancer treatment.

DISCUSSION

We identified four cases of catastrophic antiphospholipid syndrome (two with histopathological confirmation and two probable). In all four cases the patients were being treated for cancer and the CAPS was induced by a trigger: infection and/or surgery. In one case the patient presented with a hemorrhagic event, which later progressed to thrombosis, while thrombotic events were the primary factor in the other three.

As mentioned earlier, thrombosis is a multifactorial event that occurs commonly in patients being treated for cancer [1-3]. While the main mechanism responsible for the events is not fully elucidated, some factors are known. First, the occurrence of thrombotic events may result from the mutation of genes responsible for the production of substances capable of modulating coagulation and/or the process of fibrinolysis; alternatively, secondary to the development of such resistance to anticoagulants, an increase in procoagulant factors or appearance of antiphospholipid antibodies occurs [9-11].

Additionally, it is already known that during cancer growth the clotting system is modulated towards facilitating development of the neoplasia. These changes result from the expression of tissue factor by neoplastic cells, leading to the induction of angiogenesis [6,12,13]. An increase in thrombin generation (produced as a result of tissue factor expression or an enzyme called cancer pro-coagulant that directly activates factor X) not only induces angiogenesis but also leads to an increase in the metastatic potential of the cell and tissue remodeling through proteinase-activated receptors [14-17].

Another important factor is the effect of the inflammatory response generated by both the tumor and the infection. Increased cytokine levels due to infection or to tissue damage

caused by cancer treatment will act directly on the balance of the coagulation system, facilitating the onset of thrombosis. Furthermore, during the inflammatory process it is common to observe increased levels of coagulation factors (fibrinogen and factor VIII) at pro-thrombotic levels, as well as extracellular DNA traps and microvesicles that are also associated with an increased risk of thrombosis [18-23].

Other factors often associated with cancer are smoking, obesity, use of hormones (mainly in women), and surgery. These factors are also associated with the development of thrombosis. Accordingly, the cancer patient's hypercoagulable state can serve as a trigger for factors such as antiphospholipid antibodies that, in turn, generate more severe thrombotic events [14,23,24].

This article describes four patients with lupus anticoagulant (three adults and one child) who, due to the hypercoagulable state generated not only by the neoplasm but by their treatment (surgery) and complications (infection), developed a CAPS-like syndrome, a rare variant of antiphospholipid syndrome and a frequent occurrence in cancer patients [8-11]. This finding is significant since it suggests a strong interaction between the immune system and the coagulation system, and this effect may play an important role both in the onset as well as the exacerbation of autoimmune diseases or clotting disturbances (thrombosis and hemorrhagic findings).

The second case clearly illustrates how the development of a coagulation disorder not only evolved with bleeding but was also an organic solid thrombosis with characteristics of probable CAPS. However, since we believe that autoimmune diseases are defects in the regulation of immune response and we have evidence that certain components of the coagulation feedback interfere in the immune system (such as anticoagulant protein C and pro-coagulant thrombin, through proteinase-activated receptors), we suggest that autoimmunity may be generated in some cancer patients by a mismatch of the antineoplastic immune phenomenon (and its complications) exacerbated by pro-coagulant stimuli that occur in the patient. This can be observed in patient 1, who met the criteria for probable CAPS, associated with findings of autoimmunity such as marantic endocarditis.

Many stimuli can lead to hypercoagulability and thrombotic events (vascular phenomena such as stroke, myocardial infarction and pulmonary embolism are major causes of death in the Western world), and thrombosis is very frequent in patients with autoimmune diseases [19].

We conclude that the interaction between the immune and coagulation systems may be an important factor for the development of some autoimmune diseases. Further studies to better understand the effect of this interaction and its role in autoimmunity are needed, so that, if confirmed, it may generate new targets for the treatment of both autoimmune disorders and coagulation imbalances [16-20].

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References

1. Amer M. Cancer-associated thrombosis: clinical presentation and survival. *Cancer Manag Res* 2013; 26 (5): 165-78.
2. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood* 2013; 122 (10):1712-23. (Epub ahead of print)
3. de Meis E, Pinheiro VR, Zamboni MM, et al. Clotting, immune system, and venous thrombosis in lung adenocarcinoma patients: a prospective study. *Cancer Invest* 2009; 27 (10): 989-97.
4. Soff GA. Pathophysiology and management of thrombosis in cancer: 150 years of progress. *J Thromb Thrombolysis* 2013; 35 (3): 346-51.
5. Schaffner F, Yokota N, Ruf W. Tissue factor proangiogenic signaling in cancer progression. *Thromb Res* 2012; 129 (Suppl 1): S127-31.
6. De Meis E, Pinheiro VR, Loures MA, et al. Lupus anticoagulant activity as a thrombosis risk factor in lung adenocarcinoma patients. *Ann N Y Acad Sci* 2007; 1107: 51-5.
7. Font C, Vidal L, Espinosa G, et al. Solid cancer, antiphospholipid antibodies, and venous thromboembolism. *Autoimmun Rev* 2011; 10 (4): 222-7.
8. Salluh JI, Soares M, De Meis E. Antiphospholipid antibodies and multiple organ failure in critically ill cancer patients. *Clinics* 2009; 64 (2): 79-82.
9. Cervera R, Espinosa G. Update on the catastrophic antiphospholipid syndrome and the "CAPS Registry." *Semin Thromb Hemost* 2012; 38 (4): 333-8.
10. Vora SK, Asherson RA, Erkan D. Catastrophic antiphospholipid syndrome. *J Intensive Care Med* 2006; 21 (3): 144-59.
11. Morange P-E, Trégouët DA. Current knowledge on the genetics of incident venous thrombosis. *J Thromb Haemost* 2013; 11 (Suppl 1): 111-21.
12. Bergendal A, Bremme K, Hedenmalm K, et al. Risk factors for venous thromboembolism in pre-and postmenopausal women. *Thromb Res* 2012; 130 (4): 596-601.
13. Key NS. Bench to bedside: new developments in our understanding of the pathophysiology of thrombosis. *J Thromb Thrombolysis* 2013; 35 (3): 342-5.
14. Greaves M. Antiphospholipid antibodies and thrombosis. *Lancet* 1999; 353: 1348-53.
15. Ruff W. Tissue factor and cancer. *Thromb Res* 2012; 130: S84-7.
16. Ramachandran R, Hollenberg MD. Proteinases and signalling: pathophysiological and therapeutic implications via PARs and more. *Br J Pharmacol* 2008; 153: S263-82.
17. Arora P, Ricks T K, Trejo J. Protease-activated receptor signalling, endocytic sorting and dysregulation in cancer. *J Cell Sci* 2007; 120: 921-8.
18. Demers M, Wagner DD. Neutrophil extracellular traps: a new link to cancer-associated thrombosis and potential implications for tumor progression. *Oncoimmunology* 2013; 2 (2): e22946.
19. Levi M, van der Poll T, Schultz M. Infection and inflammation as risk factors for thrombosis and atherosclerosis. *Semin Thromb Hemost* 2012; 38: 506-14.
20. Schulz C, Engelmann B, Massberg S. Crossroads of coagulation and innate immunity: the case of deep vein thrombosis. *J Thromb Haemost* 2013; 11 (Suppl 1): 233-41.
21. Bertina RM. Elevated clotting factor levels and venous thrombosis. *Pathophysiol Haemost Thromb* 2003; 33 (5-6): 395-400.
22. Lacroix R, Dubois C, Leroyer AS, Sabatier F, Dignat-George F. Revisited role of microparticles in arterial and venous thrombosis. *J Thromb Haemost* 2013; 11 (Suppl 1): 24-35.
23. Cannegieter SC, van Hylckama Vlieg A. Venous thrombosis: understanding the paradoxes of recurrence. *J Thromb Haemost* 2013; 11 (Suppl 1): 161-9.
24. Bergendal A, Bremme K, Hedenmalm K, et al. Risk factors for venous thromboembolism in pre-and postmenopausal women. *Thromb Res* 2012; 130 (4): 596-601.