

Thrombosis and Cancer : Trousseau's Syndrome Revisited

'I have long been struck with the frequency with which cancerous patients are affected with painful oedema in the superior or inferior extremities, whether one or other was the seat of cancer. This frequent occurrence of phlegmasia alba dolens with an appreciable cancerous tumour, led me to the inquiry whether a relationship of cause and effect did not exist between the two....'

This statement was described by Armand Trousseau, a famous French physician, in 1865¹. Since his original description, plenty of studies have confirmed this phenomenon, though the mechanism and function of abnormal blood coagulation in cancer remain unclear.

High risk of thromboembolic disease in cancer patients is well recognised as a consequence of operations or chemotherapy². This could effect the survival of patients. Prophylactic antithrombotic agents are routinely used for cancer patients in western countries. Interestingly, this group of patients were found to carry a longer survival³. How can we explain this unexpected finding? Is the reduction in death from decreasing of thromboembolic diseases, the direct effect of antithrombotic agents? Is there any possibility that tumour biology might be altered by the antithrombotic agents which interfere the cascades of several proteases?

There are some patients who present with

spontaneous venous thrombosis and subsequently develop cancer⁴. One of the milestone studies was published in the New England Journal of Medicine by Prandoni et al⁵. They found that 7.6 % of patients with deep vein thrombosis (DVT) without a detectable primary cause developed clinically overt cancer within 2 years. The incidence of cancer was even higher among the patients who had recurrent DVT (17%). Recent studies by Baron⁶ and Sorensen⁷ also supported the strong association between thrombosis and cancer.

Other evidences linking thrombosis with cancer consist of both obvious clinical findings and laboratory research. Fifty percents of cancer patients have one or more abnormality in laboratory parameters of haemostasis, and the incidence rises to 90% in those with metastatic cancer⁸. The high levels of tissue factor and thrombin-antithrombin III but not factor XII have been detected in plasma samples of cancer patients⁹. This finding indicates that the extrinsic pathway of blood coagulation is activated in cancer patients.

If the activation of blood coagulation involves in tumour biology in the way that it could aggravate the tumour potential, the inhibition of this process should be the alternative or adjuvant treatments of choice for cancer patients. Again, several studies seem to support this hope. In experimental tumour models, the anticoagulant

therapy can reduce metastasis¹⁰. Adjuvant warfarin therapy could prolong survival in lung cancer patients¹¹. In a study of 1,250 patients undergoing major abdominal surgery for cancer at the King's College Hospital in London, those who received thromboprophylaxis with unfractionated heparin had a lower mortality rate at 3 years (9.2% vs. 21.4%, $p = 0.02$) compared with control patients¹². Another study showed a marked reduction in late cancer death within six months by low molecular weight heparin (11% vs. 31%, $p = 0.005$)¹³. The mechanism by which perioperative heparin therapy inhibits late death from metastatic cancer is unexplained.

To date, the overwhelming information unhindered by the development of molecular biology technology has opened up the understanding in natural behaviour of tumour. Mechanisms by which antithrombotic drugs may influence tumour biology was postulated. The expression of tissue factor by tumour cells was shown to associate with enhancing of growth, invasion, metastasis and angiogenesis¹⁴. The signalling pathway of tissue factor activates blood coagulation through the downstream serine proteases. This pathway might

work in autocrine and paracrine fashion and possibly activate across the cascade to affect several mediators such as cytokines and growth factors¹⁵.

One of the considerable natural history of the tumour is that its ability to generate proteolytic factors and adhesion molecules which are essential for tumour growth, invasion, angiogenesis and metastasis. Recent discovery of survivin, a gene thought to inhibit apoptosis (programmed cell death), may be another jigsaw linking thrombosis to cancer, because its cDNA sequence is equivalent to the antisense sequence of coagulation factor X, a central factor in common pathway of blood coagulation¹⁶.

The interaction between tumour cells and extracellular matrix of host involves in the balance between the series of proteolytic cascades and fibrinolytic reactions. Numbers of activators and inhibitors of proteases and fibrinolytic enzymes have been demonstrated to involve in the complex mechanism of growth, invasion, angiogenesis and metastasis of tumour¹⁷. Thus, the interference of blood coagulation activation conveyed by tumour cells may be a new weapon for fighting with cancer.

Vitoon Chinswangwatanakul M.D., Ph.D.

Department of Surgery,

Faculty of Medicine Siriraj Hospital,

Bangkok.

REFERENCES :

1. Trousseau A. Plegmasia alba dolens. In: Anonymous Clinique Medicale de l'Hotel Dieu de Paris (Lectures on Clinical Medicine). 1868 ed. London: The New Sydenham Society, 1865: 281-332.
2. Kakkar AK, Williamson RC. Thromboprophylaxis in malignant disease. Br J Surg 1995; 82: 724-5.
3. Chahinian AP, Probert KJ, Ware JH, Zimmer B, Perry MC, Hirsh V, et al. A randomized trial of anticoagulation

- with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and Leukemia Group B. *J Clin Oncol* 1989; **7**: 993-1002.
4. Monreal M, Fernandez-Llamazares J, Perandreu J, Urrutia A, Sahuquillo JC, Contel E. Occult cancer in patients with venous thromboembolism: which patients, which cancers. *Thromb Haemost* 1977; **78**: 1316-18.
 5. Prandoni P, Lensing AW, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992; **327**: 1128-33.
 6. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. *Lancet* 1998; **351**: 1077-80.
 7. Sorensen HT, Mellemejaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998; **338**: 1169-73.
 8. Nand S, Messmore H. Hemostasis in malignancy. *Am J Hematol* 1990; **35**: 45-55.
 9. Kakkar AK, DeRuvo N, Chinswangwatanakul V, Tebbutt S, Williamson RC. Extrinsic-pathway activation in cancer with high factor VIIa and tissue factor. *Lancet* 1995; **346**: 1004-5.
 10. Agostino D, Clifton EE. Anticoagulants and the development of pulmonary metastases. *Arch Surg* 1962; **84**: 449-53.
 11. Zacharski LR, Henderson WG, Rickles FR, et al. Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. Final report of VA Cooperative Study #75. *Cancer* 1984; **53**: 2046-52.
 12. Kakkar AK, Hedges AR, Williamson RCN, Kakkar VV. Perioperative heparin therapy inhibits late death from metastatic cancer. *Inter J Oncol* 1995; **6**: 885-8.
 13. Green D, Hull RD, Brant R, Pineo GF. Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin. *Lancet* 1992; **339**: 1476.
 14. Ruf W, Mueller BM. Tissue factor in cancer angiogenesis and metastasis. *Curr Opin Hematol* 1996; **3**: 379-84.
 15. Kakkar AK, Lemoine NR, Stone SR, Altieri D, Williamson RCN. Identification of a thrombin receptor with factor Xa receptor and tissue factor in human pancreatic carcinoma cells. *J Clin Pathol Mol Pathol* 1995; **48**: M288-M290.
 16. Li F, Altieri DC. The cancer antiapoptosis mouse survivin gene: characterization of locus and transcriptional requirements of basal and cell cycle-dependent expression. *Cancer Res* 1999; **59**(13): 3143-51.
 17. Zacharski LR, Wojtukiewicz MZ, Costantini V, Ornstein DL, Memoli VA. Pathways of coagulation/fibrinolysis activation in malignancy. *Semin Thromb Hemost* 1992; **18**: 104-16.