Trousseau's syndrome: multiple definitions and multiple mechanisms

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In 1865, Armand Trousseau noted that unexpected or migratory thrombophlebitis could be a forewarning of an occult visceral malignancy. An analysis by Sack and colleagues in 1977 extended the term Trousseau's syndrome to include chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis, and arterial emboli in patients with cancer, often occurring with mucin-positive carcinomas. In recent times the term has been ascribed to various clinical situations, ranging all the way from these classic descriptions to any kind of coagulopathy occurring in the setting of any kind of malignancy. These multiple definitions of Trousseau's syndrome are partly the consequence of multiple pathophysiologic mechanisms that apparently contribute to the hypercoagulability associated with cancer. Even the classic syndrome probably represents a spectrum of disorders, ranging from exaggerated fluid-phased thrombosis dependent on prothrombotic agents such as tissue factor to a platelet- and endotheliumum-based selectin-dependent microangiopathy associated with mucin-producing carcinomas, along with thrombin and fibrin production. Also considered here are recent hypotheses about genetic pathways within tumor cells that might trigger these thrombotic phenomena, and the reasons why therapy with heparins of various kinds remain the preferred treatment, probably because of their salutary actions on several of the proposed pathologic mechanisms. (Blood. 2007;110: 1723-1729)

Introduction

Trousseau's syndrome is well known to clinicians, partly because Armand Trousseau not only described it in 1865[1] but also diagnosed the syndrome on himself 2 years later, succumbing shortly thereafter to a gastric cancer.[2,3] The association between cancer and excessive blood coagulation remains well-recognized, forming the basis of many reviews, monographs, symposia, and international conferences. Most of these begin by mentioning Trousseau and his eponymous syndrome. Trousseau made an astute clinical observation, noting that some patients who presented with unexpected, unusual, or migratory thromboses later manifested a visceral malignancy. This description was refined and extended over the years, culminating in a classic review by Sack et al,[4] in which Trousseau's syndrome was reported as being frequently associated with chronic disseminated intravascular coagulopathy, platelet-rich microthrombi, microangiopathic hemolytic anemia, verrucous endocarditis, and thromboembolic problems related to these processes. In more recent times, many patients are diagnosed with Trousseau's syndrome even if they do not manifest these classic features, and the definition has included those presenting primarily with uncomplicated lower limb deep venous thrombosis. The term is sometimes even applied to patients who already have an advanced malignancy and then develop some form of thrombosis. Although similar mechanisms may be operating, such advanced cases often have other reasons for a thrombotic tendency, such as immobility, dehydration, mechanical compression of veins, infectious processes, chemotherapy, and so forth.

What is Trousseau's syndrome?

Despite its frequent mention in reviews,[4-17] the term Trousseau's syndrome is not in the MeSH headings of Medline or PubMed. Literature searching is confounded by the insistence of some journal editors on using "Trousseau syndrome."[18] Thus, searching Pubmed for Trousseau's syndrome and Trousseau syndrome yields mostly nonoverlapping hits. Such searches, along with review of web-based sources, yield definitions of Trousseau's syndrome ranging from "occurrence of thrombophlebitis migrans with visceral cancer" and, "spontaneous recurrent or migratory venous thromboses and/or arterial emboli caused by nonbacterial thrombotic endocarditis in a patient with malignancy" all the way to simply "carcinoma-induced coagulopathy," "hypercoagulability syndrome associated with cancer," "malignancy-related thromboembolism," "idiopathic thromboembolism associated with cancer," and "malignancy-related hypercoagulability." On the basis of the actual history, it seems reasonable to restrict use of Trousseau's syndrome to unexplained thrombotic events that precede the diagnosis of an occult visceral malignancy or appear concomitantly with the tumor. As discussed in this review, even this restricted definition encompasses a spectrum of disorders in which multiple overlapping mechanisms are probably involved.

Early theories about mechanisms of Trousseau's syndrome

When thromboses occur in the setting of occult carcinomas, it is reasonable to speculate that tumor products entering the bloodstream are primarily responsible. The association of the syndrome with mucin-producing carcinomas initially suggested that mucins were the underlying trigger.[19] Mucins are highly glycosylated secretory products of epithelial cells that become aberrantly glycosylated in carcinomas and then are inappropriately secreted into the bloodstream.[20-24] However, not all cases of Trousseau's syndrome are associated with mucin-producing carcinomas.[4] Furthermore, although studies of experimental mucin injection into

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animals were encouraging,[19,25] they were probably confounded because mucins are large sticky molecules, making it difficult to free preparations from contaminating cytokines or other bioactive agents, particularly tissue factor (TF), a primary cellular initiator of fluid-phase blood coagulation.[26] Meanwhile, TF itself was also considered a cause of Trousseau's syndrome[27] and found at high concentrations in many malignancies,[28,29] including instances when the primary tumor was extremely small and yet able to induce major systemic thromboses.[26] Also described was a cysteine proteinase from carcinoma extracts, which directly activated factor X.[30-32] Such findings suggested that activators of fluid-phase coagulation were the key to the pathogenesis.[9-17] This review concludes that Trousseau's syndrome is actually a spectrum of disorders and considers additional molecular mechanisms that have more recently pointed to pathways for its initiation. This is done recognizing how little we still understand about this syndrome, and yet how important it is to seek a better understanding of it.

Tissue factor

In addition to cases of Trousseau's syndrome involving carcinomas rich in TF, elevated TF expression by the associated angiogenic endothelium has been reported. Activated oncogenes (K-ras, EGFR, PML-RARA, and MET) or inactivated tumor suppressors (eg, p53 or PTEN) also lead to an induction in TF levels and activity, which is postulated to promote not only hypercoagulability but also tumor aggressiveness and angiogenesis.[14-16] The thrombin receptor (protease-activated receptor-1) is also up-regulated in cancer cells expressing oncogenic K-ras.[33] The question arises as to how the tumor-derived TF becomes exposed to the fluid-phase coagulation system, starting with circulating factor VII. In classic studies, histologic evidence of direct contact between a TF-rich tumor and the bloodstream seem to be associated with Trousseau's syndrome,[26] suggesting that the TF might be acting locally. Considering current understanding of TF biology and its membrane-associated nature,[15,34,35] TF-containing membrane fragments or microvesicles produced by tumor cells would appear to be a more likely cause of distant thromboses. Although this mechanism remains speculative, earlier studies did show shed plasma membrane vesicles with procoagulant activity derived from syngeneic carcinomas cultured in vitro or grown in ascites form in vivo,[36] as well as in the plasma of patients with certain types of leukemia.[37] More recently, mouse models have shown that the oncogene and tumor-suppressor gene status of xenograft tumors are determinants of circulating (presumably microvesicle-associated) TF activity in the blood of the immunodeficient mice.[15,33] Regardless of the originating mechanisms, it is likely that conversion of factor VII (FVII) to its active form (FVIIa) in complex with TF triggers the production of other coagulation-related proteases, particularly FXa and FIXa. Factor Xa then works with FVa to cleave circulating prothrombin and generate thrombin, which is required not only to generate fibrin and activate platelets but also to facilitate amplification through further generation of other active clotting factors such as FVIIIa and FXIa (Figure 1). Although all these mechanisms involving TF and thrombin seem reasonable, more studies are needed to directly show their role in patients with Trousseau's syndrome.

Tumor-associated cysteine proteinase

As mentioned above, Falanga and Gordon[30] reported a cysteine protease ("cancer procoagulant" or CP) that directly activated factor X in the absence of factor VII, and this activity was later reported in many natural human tumors.[38,39] However, there is some question as to whether this is due to contamination with traces of TF/VIIa complexes. A study of such preparations using anti-TF antibodies noted crossreactive proteins,[32] and the researchers concluded that "it seems possible that cancer procoagulant preparations contain proteins that have some epitopes similar to the epitopes recognized in tissue factor by antitissue factor monoclonal antibodies (Mabs). However, these proteins do neither have the molecular weight nor the amino acid sequence of tissue factor." A recent clinical study evaluated prothrombotic markers and their relation to CP concentration in the blood of patients with gastrointestinal adenocarcinomas with or without metastatic disease.[40] The data suggested that CP is only a minor risk factor for deep venous thrombosis in such patients. However, more studies of this matter are needed.

Mechanisms involving tumor hypoxia

In 2001, Denko and Giaccia[8] proposed that tumor hypoxia represented the "physiologic link between Trousseau's syndrome and tumor metastasis." Although unaccompanied by direct experimental support, the researchers made a strong case that tumor cells under microenvironmental stress are likely to produce procoagulant and angiogenic factors. They specifically suggested that hypoxia (decreased oxygenation) could increase the expression of genes that facilitate coagulation, including tissue factor and plasminogen activator inhibitor type 1 (PAI-1). These researchers also proposed a link between these prothrombotic processes and metastatic disease, revisiting the well-known observation that the two phenomena share much in common.

Carcinomas mucins

Early in vivo studies of carcinoma mucins[19,25] were probably confounded by contamination with other bioactive factors, including TF. Carcinoma mucins are large, heavily glycosylated molecules[20-24] and are often carriers of sialylated, fucosylated, sulfated glycans that can act as ligands for the selectins.[41,42] Such selectin-mucin interactions seem to be involved in the hematogenous phase of tumor metastasis.[42-45] Mixtures of these abnormal carcinoma mucins (or their proteolytic fragments or both) are also shed by tumors and can be found in the bloodstream of patients with cancer,[46-53] where their levels are sometimes measured as prognostic markers. Thus, it remained reasonable to suggest that mucins are involved in Trousseau's syndrome.

One way to eliminate contamination is to take advantage of the fact that tumor mucins contain heavily glycosylated segments that are resistant to denaturation, boiling, and even proteases. Thus, when human colon carcinoma xenograft extracts were treated with multiple enzymes (including broad-spectrum proteases) followed by boiling and denaturation, the only surviving macromolecules were fragments of heavily glycosylated mucins.[18] These preparations were free of TF or endotoxin and were incapable of accelerating clotting in vitro. However, they rapidly induced disseminated platelet-rich microthrombi when injected intravenously into normal mice. These occurred even when animals were pretreated with amounts of hirudin sufficient to block in vivo thrombin formation (although as expected, the associated fibrin deposition did not occur). Moreover, this platelet aggregation was dependent on P-selectin and L-selectin, as determined using genetically deficient mice.[18] This is consistent with prior findings that carcinoma mucins have binding sites for both P- and L-selectins.[42] Further studies indicated a stepwise process in which

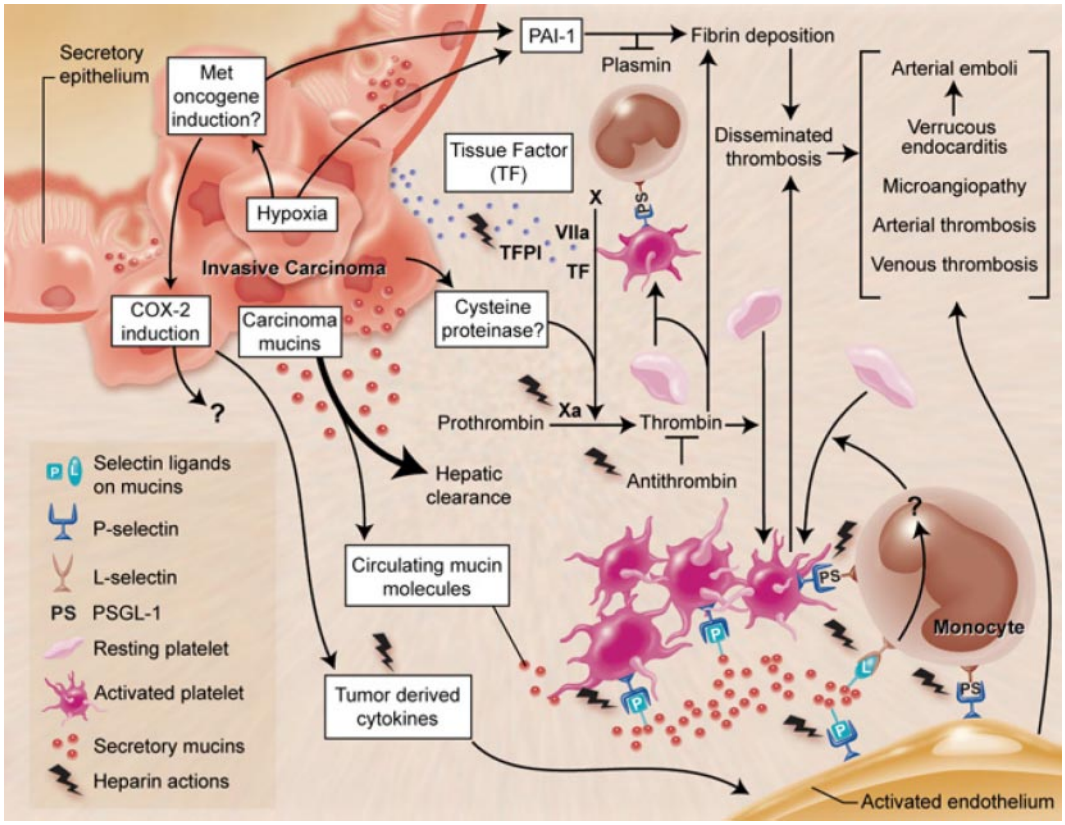

Figure 1. Multiple mechanisms in Trousseau's syndrome. There are multiple overlapping and interacting mechanisms that can explain the increased incidence of thrombosis in patients with malignancies. In Trousseau's syndrome, hypercoagulability manifests even before the diagnosis of the tumor and is probably the result of products arising from the tumor itself. The most common malignancies associated with this syndrome are carcinomas (cancers of epithelial origin) that are often, but not always, mucin producing. This cartoon depicts a mucin-producing carcinoma arising in a hollow organ, which secretes mucins with altered glycans inappropriately into the bloodstream. Although the bulk of these mucins are probably rapidly cleared by the liver, a small fraction are resistant to clearance and can interact with P- and L-selectins, inducing the formation of platelet-rich microthrombi by multiple pathways. Exposure of tissue factor (TF)–rich tumor cell surfaces to the bloodstream or the release of TF-rich microvesicles by the tumor is presumed to induce fibrin formation and platelet aggregation by thrombin production. There is some evidence for a cysteine proteinase secreted by carcinoma cells that can directly activate factor X to generate thrombin. Although interactions of platelet and endothelial P-selectin with P-selectin glycoprotein ligand-1 (PSGL-1) on monocytes may further contribute to these reactions, the exact mechanism by which mucins eventually generate thrombin and fibrin production is unknown. Hypoxic conditions within the tumor, the expression of the MET oncogene, or both might also enhance production of procoagulant factors such as TF and plasminogen activator inhibitor-1 (PAI-1), and tumor-derived inflammatory cytokines may serve to activate endothelial and platelet adhesion molecules. Various combinations of these mechanisms can help explain the unusual, migratory, and exaggerated thrombotic phenomena of Trousseau's syndrome. As indicated in the figure, heparin has potential salutary effects on many of the relevant processes. This may explain why heparin preparations of various kinds are the preferred agent for the management of Trousseau's syndrome.

the mucins initially activate leukocytes by L-selectin ligation, generating an as yet unknown mediator, which then cooperates with the mucins interacting with P-selectin on endothelium or platelets or both, ultimately generating the platelet-rich microthrombi (Figure 1), including fibrin deposition, by an as yet unknown mechanism. Interestingly, although the formation of the platelet clumps themselves could not be abrogated by thrombin inhibitors such as hirudin, it was efficiently blocked by heparin. This is consistent with the finding that heparin (at concentrations acceptable in clinical practice) is a potent inhibitor of P- and L-selectin interactions with natural or carcinoma ligands.[42,54,55]

The great majority of such injected carcinoma mucins were rapidly cleared by multiple glycan receptors in the mouse liver.[56] The small amounts surviving clearance were heavily sialylated, and presumably represented the fraction mediating the pathologic reactions with platelets and leukocytes. Thus, patients with carcinomas probably secrete large quantities of mucins into circulation, which are rapidly cleared, leaving behind only the proverbial "tip of the iceberg" in the bloodstream. The pathologic processes triggered by such carcinoma mucins require not only altered glycosylation but also inappropriate secretion into the vascular compartment. Thus, mucins might also enter the bloodstream in nonmalignant processes involving mucin-secreting organs. Could this help explain the high frequency of venous thrombosis in inflammatory bowel disease?[57] Elevated levels of serum mucin antigens are also associated with hepatocellular disease and liver cirrhosis. Because the liver itself does not produce mucins, this may represent failure of the mucin clearance system to remove the low levels of mucins that normally spill into the blood from hollow organs. This is also a potential explanation for the "false positive" tumor marker studies[58] and the unexplained coagulopathies seen in patients with chronic liver disease.[59]

Mechanisms involving oncogene activation

In 2005, Boccaccio et al[60] stated that Trousseau's syndrome had "so far resisted a mechanistic explanation." Although this claim was at odds with prior literature, the researchers did present a truly novel mechanism, using a mouse model in which targeting an activated human MET oncogene to adult mouse liver caused slowly progressing hepatocarcinogenesis, which was preceded and accompanied by a syndrome "manifesting first with blood hypercoagulation (venous thromboses), and then evolving toward fatal internal hemorrhages." Following up on these observations, these investigators showed that the pathogenesis of this model syndrome was driven by the transcriptional response to the *MET* oncogene,

especially involving up-regulation of *PAI-1* and cyclooxygenase-2 (*COX-2*) genes. Because both molecules can theoretically support a thrombohemorrhagic phenotype, they concluded that they had found "direct genetic evidence for the long-sought-after link between oncogene activation and hemostasis." They later went on to point out that hypoxia could induce Met oncogene transcription, suggesting that this provided "a clinically important perspective on malignant invasion and metastasis."[61] However, as with all earlier mechanisms described above, this one also requires validation in the natural clinical setting of patients with Trousseau's syndrome.

Spectrum of overlapping mechanisms in Trousseau's syndrome

It is reasonable to suggest that all these proposed mechanisms represent a range of overlapping pathways that contribute to various extents toward the thromboembolic diathesis in patients with tumors (Figure 1.). Thus, Trousseau's syndrome is better considered a spectrum of disorders, ranging at one extreme with thrombosis induced primarily by the production of TF by tumor cells, all the way to a platelet-rich microthrombotic process triggered by carcinoma mucins and involving P- and L-selectins. Other mechanisms proposed about hypoxia, oncogene activation, and so forth, can fit into this spectrum of pathways, as shown in Figure 1, all eventually resulting in thrombin generation and fibrin deposition. An additional possibility not explored is activation of endothelium by tumor-derived inflammatory cytokines, which could induce expression of various adhesive molecules such as V-CAM and E-selectin.

Management of Trousseau's syndrome

Regardless of underlying mechanisms, the primary approach to treating Trousseau's syndrome is to eliminate the causative tumor, if possible. Although this is often not feasible, the one recurring theme in the literature is that heparin is the preferred treatment, and that specifically blocking factor Xa or thrombin is insufficient in many instances.[4,62-66] Indeed, there are many reports of marked and even catastrophic acceleration of thrombosis on discontinuation of heparin in Trousseau's syndrome.[4,26,62,67] Taken together with the relative inactivity of vitamin K antagonists or direct thrombin inhibitors in some cases, it is reasonable to suggest that this heparin activity is mediated by more than just its ability to inactivate thrombin by enhancement of antithrombin.

Why are heparins the preferred treatment in Trousseau's syndrome?

Although originally isolated and approved for clinical use as an anticoagulant, unfractionated heparin is actually a complex and heterodisperse mixture of glycosaminoglycans extracted from certain animal sources.[68-71] The serpin antithrombin binds to a specific modified pentasaccharide sequence that is distributed sporadically within long heparin chains,[70] markedly enhancing its ability to irreversibly inactivate both activated factor Xa and thrombin, thereby interrupting fluid-phase thrombosis, as well as secondary platelet activation. However, as shown in Figure 1, heparin preparations have a variety of other biologic activities that can help explain its beneficial effects in Trousseau's syndrome. Perhaps this is why heparins have remained the preferred treatment for Trousseau's syndrome. In this regard, it is worth noting that modern therapeutic approaches have tended to become more and more specific, being highly targeted toward defined molecular mechanisms. In fact, complex clinical situations such as Trousseau's syndrome may be better managed by drugs such as heparin, which have multiple nonoverlapping moderating actions.

Heparin-mediated interactions that are potentially beneficial in Trousseau's syndrome

In addition to antithrombin, heparins also activate two other serpins involved in blood coagulation, Heparin cofactor II[72] and protein C inhibitor.[73] Another independent heparin action is to block the binding of L- and P-selectins to their natural and pathologic ligands.[54,74-76] This interrupts carcinoma-mucin–dependent adhesion phenomena mediated by these selectins (Figure 1) as well as signaling pathways triggered by their interactions with natural ligands (eg, induction of tissue factor or platelet-activating factor synthesis in monocytes by P-selectin engagement of PSGL-1),[77,78] which is one possible explanation for the subsequent generation of thrombin and fibrin. Meanwhile, tissue factor pathway inhibitor (TFPI) is released from the vascular endothelium by heparin, perhaps delivering higher concentrations of this potent anticoagulant to the sites of ongoing thrombosis.[79-83] The effects of heparin on fibrinolysis are more complex, because both activators and inhibitors can be affected.[84,85] Heparin can also bind and potentially neutralize a wide variety of cytokines and chemokines.[86-88] Some of these inflammatory cytokines could potentially aggravate Trousseau's syndrome by activating endothelial cells, causing enhanced expression of adhesion molecules, including P-selectin.

Alternative approaches to the management of Trousseau's syndrome

In recent years low molecular weight heparins (LMWHs) have become popular, in part because of their improved pharmacokinetics, the ability to give single daily dosages, and the reduced incidence of heparin-induced thrombocytopenia.[89-91] Moreover, LMWHs selectively inhibit factor Xa without affecting thrombin and may be less likely to deplete TFPI pools over time.[79,80,82,92,93] Thus, there have been several reports in which LMWHs have been successfully substituted for unfractionated heparin in managing Trousseau's syndrome.[64,94] However, it should be noted that the ability of some LMWHs to mediate some of the heparin actions indicated in Figure 1 may not be equivalent. For example, some LMWHs of shorter length are not as effective at blocking P- and L-selectins, even at comparable levels of anti-Xa activity.[55,95] Therefore, although switching to LMWHs may be convenient and even beneficial,[96-98] further studies are needed to assure that any useful effects are not being lost when using some of them. An interesting prediction arising from recent work is that the synthetic pentasaccharide fondaparinux (Arixtra) might be least effective, even if given at doses that achieve equivalent anti–factor Xa activity.[55] This needs to be studied further. Of course, one can envisage an alternate approach, using a combination of modern anticoagulant agents that would block many of the processes thought to be involved in Trousseau's syndrome.[99] However, as with any form of combination therapy, there is an increased probability of side effects.

Risk of an occult cancer in a patient with unexplained thrombosis

By its original definition, the diagnosis of Trousseau's syndrome is made in retrospect, when the occult malignancy is found. Thus, one can ask whether there is any practical value in making a diagnosis of this syndrome. The risk of an occult carcinoma being found after an episode of otherwise unexplained venous thrombosis has ranged widely in various retrospective series. In a prospective analysis,[100] apparently cancer-free patients with acute idiopathic venous thromboembolism were randomly assigned to have either extensive screening for occult cancer or no further testing. In the former group, approximately 13% of the patients were shown to have an occult cancer. A similar number of cancers emerged in the control group during a 2-year period. As expected, malignancies found in the extensive screening group were at an earlier stage. However, cancer-related mortality during the 2-year follow-up period was not markedly different. A subsequent decision analysis of these data suggested that screening for cancer with an abdominal or pelvic computed tomography scan with or without mammography or sputum cytology appeared potentially useful for cancer screening in patients with unexplained thromboses.[101] Overall, the conclusions were that "the cost-effectiveness analysis of this strategy needs confirmation in a large trial" and that although "Data from these studies do not conclusively demonstrate that earlier diagnosis ultimately prolongs life. . . . the collective observation makes such a beneficial effect likely."[102]

There are many features in common between the pathogenesis of Trousseau's syndrome and factors that appear to facilitate tumor metastases, including roles for TF, selectins, platelets, endothelium, and fibrin.[5-8,42,60,103-105] Thus, it is likely that the thrombotic processes involved in Trousseau's syndrome also facilitate the spread of tumors. Together with the fact that advanced visceral carcinomas are mostly incurable, this may explain why the search for occult malignancies has not had a large impact on the final outcome of cancer survival.

On a related note, others have reported that middle-aged men free of malignancy who showed persistent activation of the coagulant pathway (prothrombin fragments 1 + 2 and fibrinopeptide A concentrations exceeding the upper quartiles of the population distribution in 2 consecutive annual examinations) showed a higher mortality,[106] which was largely due to cancers of the digestive tract. It is unclear whether this persistent activation of the coagulant pathway is the consequence of an occult malignancy (ie, a "preclinical Trousseau's syndrome"), or whether the hypercoagulability arising from some other cause "awakens" dormant tumor cells in the host.[107] Another interesting suggestion is that toxicity from elevated ambient body iron levels might explain this association between persistent coagulation activation and occult cancer.[108] The contribution of increased iron to tumor initiation and promotion is suggested to collaborate with the effects of iron-induced oxidative damage on lipids, which can cause increased TF expression, while down-regulating the activity of TFPI and the expression of thrombomodulin.[108]

Conclusions and future prospects

Regarding how exactly to define Trousseau's syndrome, we should recognize that it is a somewhat semantic issue. However, as articulated well by others,[3] if ever there was a case when an eponym was deserved for a clinical syndrome it is that of Trousseau, who not only made an astute clinical observation that has survived the test of time but also diagnosed it accurately on himself. Thus, it is suggested that the term Trousseau's syndrome be reserved for situations in which thrombotic problems that cannot be explained by any other obvious factor(s) occur in the setting of either an occult or a recently diagnosed carcinoma. This suggestion is made with the recognition that even in its classic form Trousseau's syndrome is probably mediated by multiple mechanisms, and that any given patient may have different combinations of overlapping and interacting mechanisms as a cause of their prothrombotic condition. In the final analysis there is still much to be learned about this syndrome and its optimal management.

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Conflict-of-interest disclosure: A.V. is cofounder and current consultant to Noble Molecules, a company seeking to bring the non–anticoagulant therapeutic benefits of heparins to the bedside.

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References

1. Trousseau A. Plegmasia alba dolens. Lectures on clinical medicine, delivered at the Hotel-Dieu, Paris. 1865;5:281-332.
2. Samuels MA, King ME, Balis U. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-2002. A 61-year-old man with headache and multiple infarcts. N Engl J Med. 2002;347:1187-1194.
3. Khorana AA. Malignancy, thrombosis and Trousseau: the case for an eponym. J Thromb Haemost. 2003;1:2463-2465.
4. Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore). 1977; 56:1-37.
5. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood. 1983;62:14-31.
6. Goad KE, Gralnick HR. Coagulation disorders in cancer. Hematol Oncol Clin North Am. 1996;10: 457-484.
7. Rickles FR, Falanga A. Molecular basis for the relationship between thrombosis and cancer. Thromb Res. 2001;102:V215-V224.
8. Denko NC, Giaccia AJ. Tumor hypoxia, the physiological link between Trousseau's syndrome (carcinoma-induced coagulopathy) and metastasis. Cancer Res. 2001;61:795-798.
9. Lee AY. Cancer and thromboembolic disease: pathogenic mechanisms. Cancer Treat Rev. 2002;28:137-140.
10. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. Lancet Oncol. 2002;3:27-34.
11. Sutherland DE, Weitz IC, Liebman HA. Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis, and treatment. Am J Hematol. 2003;72:43-52.
12. De Cicco M. The prothrombotic state in cancer: pathogenic mechanisms. Crit Rev Oncol Hematol. 2004;50:187-196.
13. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293:715-722.
14. Rickles FR. Mechanisms of cancer-induced thrombosis in cancer. Pathophysiol Haemost Thromb. 2006;35:103-110.
15. Rak J, Milsom C, May L, Klement P, Yu J. Tissue

factor in cancer and angiogenesis: the molecular link between genetic tumor progression, tumor neovascularization, and cancer coagulopathy. Semin Thromb Hemost. 2006;32:54-70.

16. Rak J, Yu JL, Luyendyk J, Mackman N. Oncogenes, Trousseau syndrome, and cancer-related changes in the coagulome of mice and humans. Cancer Res. 2006;66:10643-10646.
17. Winter PC. The pathogenesis of venous thromboembolism in cancer: emerging links with tumour biology. Hematol Oncol. 2006;24:126-133.
18. Wahrenbrock M, Borsig L, Le D, Varki N, Varki A. Selectin-mucin interactions as a probable molecular explanation for the association of Trousseau syndrome with mucinous adenocarcinomas. J Clin Invest. 2003;112:853-862.
19. Pineo GF, Brain MC, Gallus AS, Hirsh J, Hatton MW, Regoeczi E. Tumors, mucus production, and hypercoagulability. Ann N Y Acad Sci. 1974;230: 262-270.
20. Carraway KL, Fregien N, Carraway KL III, Carraway CAC. Tumor sialomucin complexes as tumor antigens and modulators of cellular interactions and proliferation. J Cell Sci. 1992;103:299-307.
21. Kim YS, Gum J, Brockhausen I. Mucin glycoproteins in neoplasia. Glycoconj J. 1996;13:693-707.
22. Perez-Vilar J, Hill RL. The structure and assembly of secreted mucins. J Biol Chem. 1999;274: 31751-31754.
23. Hanisch FG, Muller S. MUC1: the polymorphic appearance of a human mucin. Glycobiology. 2000;10:439-449.
24. Fukuda M, Tsuboi S. Mucin-type O-glycans and leukosialin. Biochim Biophys Acta. 1999;1455: 205-217.
25. Pineo GF, Regoeczi E, Hatton MW, Brain MC. The activation of coagulation by extracts of mucus: a possible pathway of intravascular coagulation accompanying adenocarcinomas. J Lab Clin Med. 1973;82:255-266.
26. Callander N, Rapaport SI. Trousseau's syndrome. West J Med. 1993;158:364-371.
27. Zacharski LR, Schned AR, Sorenson GD. Occurrence of fibrin and tissue factor antigen in human small cell carcinoma of the lung. Cancer Res. 1983;43:3963-3968.
28. Rao LV. Tissue factor as a tumor procoagulant. Cancer Metastasis Rev. 1992;11:249-266.
29. Callander NS, Varki N, Rao LV. Immunohistochemical identification of tissue factor in solid tumors. Cancer. 1992;70:1194-1201.
30. Falanga A, Gordon SG. Isolation and characterization of cancer procoagulant: a cysteine proteinase from malignant tissue. Biochemistry. 1985;24:5558-5567.
31. Gordon SG, Cross BA. A factor X-activating cysteine protease from malignant tissue. J Clin Invest. 1981;67:1665-1671.
32. Raasi S, Mielicki WP, Gordon SG, Korte W. Properties of proteins in cancer procoagulant preparations that are detected by anti-tissue factor antibodies. Arch Biochem Biophys. 2004;428:131-135.
33. Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. Blood. 2005;105:1734-1741.
34. Giesen PL, Nemerson Y. Tissue factor on the loose. Semin Thromb Hemost. 2000;26:379-384.
35. Polgar J, Matuskova J, Wagner DD. The P-selectin, tissue factor, coagulation triad. J Thromb Haemost. 2005;3:1590-1596.
36. Dvorak HF, Quay SC, Orenstein NS, et al. Tumor shedding and coagulation. Science. 1981;212: 923-924.
37. Carr JM, Dvorak AM, Dvorak HF. Circulating membrane vesicles in leukemic blood. Cancer Res. 1985;45:5944-5951.
38. Donati MB, Gambacorti-Passerini C, Casali B, et al. Cancer procoagulant in human tumor cells: evidence from melanoma patients. Cancer Res. 1986;46:6471-6474.
39. Grignani G, Falanga A, Pacchiarini L, et al. Human breast and colon carcinomas express cysteine proteinase activities with pro-aggregating and pro-coagulant properties. Int J Cancer. 1988; 42:554-557.
40. KaŸmierczak M, Lewandowski K, Wojtukiewicz MZ, et al. Cancer procoagulant in patients with adenocarcinomas. Blood Coagul Fibrinolysis. 2005;16:543-547.
41. Kim YJ, Borsig L, Han HL, Varki NM, Varki A. Distinct selectin ligands on colon carcinoma mucins can mediate pathological interactions among platelets, leukocytes, and endothelium. Am J Pathol. 1999;155:461-472.
42. Varki NM, Varki A. Heparin inhibition of selectin-mediated interactions during the hematogenous phase of carcinoma metastasis: rationale for clinical studies in humans. Semin Thromb Hemost. 2002;28:53-66.
43. Kim YJ, Borsig L, Varki NM, Varki A. P-selectin deficiency attenuates tumor growth and metastasis. Proc Natl Acad Sci U S A. 1998;95:9325-9330.
44. Borsig L, Wong R, Feramisco J, Nadeau DR, Varki NM, Varki A. Heparin and cancer revisited: mechanistic connections involving platelets, P-selectin, carcinoma mucins, and tumor metastasis. Proc Natl Acad Sci U S A. 2001;98:3352-3357.
45. Borsig L, Wong R, Hynes RO, Varki NM, Varki A. Synergistic effects of L- and P-selectin in facilitating tumor metastasis can involve non-mucin ligands and implicate leukocytes as enhancers of metastasis. Proc Natl Acad Sci U S A. 2002;99: 2193-2198.
46. Singhal AK, Orntoft TF, Nudelman E, et al. Profiles of Lewis X-containing glycoproteins and glycolipids in sera of patients with adenocarcinoma. Cancer Res. 1990;50:1375-1380.
47. Kawa S, Kato M, Oguchi H, Kobayashi T, Furuta S, Kanai M. Preparation of pancreatic cancer-associated mucin expressing CA19–9, CA50, Span-1, sialyl SSEA-1, and Dupan-2. Scand J Gastroenterol. 1991;26:981-992.
48. Hanski C, Hanski M-L, Zimmer T, Ogorek D, Devine P, Riecken E-O. Characterization of the major sialyl-Lex-positive mucins present in colon, colon carcinoma, and sera of patients with colorectal cancer. Cancer Res. 1995;55:928-933.
49. Zhang K, Baeckström D, Brevinge H, Hansson GC. Secreted MUC1 mucins lacking their cytoplasmic part and carrying sialyl-Lewis a and x epitopes from a tumor cell line and sera of colon carcinoma patients can inhibit HL-60 leukocyte adhesion to E-selectin-expressing endothelial cells. J Cell Biochem. 1996;60:538-549.
50. Yiannakou JY, Newland P, Calder F, Kingsnorth AN, Rhodes JM. Prospective study of CAM 17.1/WGA mucin assay for serological diagnosis of pancreatic cancer. Lancet. 1997;349:389-392.
51. Komatsu M, Arango ME, Carraway KL. Synthesis and secretion of Muc4/sialomucin complex: implication of intracellular proteolysis. Biochem J. 2002;368:41-48.
52. Rhodes JM. Usefulness of novel tumour markers. Ann Oncol. 1999;10(suppl 4):118-121.
53. Yin BWT, Lloyd KO. Molecular cloning of the CA125 ovarian cancer antigen: identification as a new mucin, MUC16. J Biol Chem. 2001;276: 27371-27375.
54. Koenig A, Norgard-Sumnicht KE, Linhardt R, Varki A. Differential interactions of heparin and heparan sulfate glycosaminoglycans with the selectins: implications for the use of unfractionated and low molecular weight heparins as therapeutic agents. J Clin Invest. 1998;101:877-889.
55. Stevenson JL, Choi SH, Varki A. Differential metastasis inhibition by clinically relevant levels of heparins–correlation with selectin inhibition, not antithrombotic activity. Clin Cancer Res. 2005;11: 7003-7011.
56. Wahrenbrock MG, Varki A. Multiple hepatic receptors cooperate to eliminate secretory mucins aberrantly entering the bloodstream: are circulating cancer mucins the "tip of the iceberg"? Cancer Res. 2006;66:2433-2441.
57. Srirajaskanthan R, Winter M, Muller AF. Venous thrombosis in inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2005;17:697-700.
58. DiBaise JK, Donovan JP. Markedly elevated CA125 in hepatic cirrhosis: two case illustrations and review of the literature. J Clin Gastroenterol. 1999;28:159-161.
59. Mammen EF. Coagulopathies of liver disease. Clin Lab Med. 1994;14:769-780.
60. Boccaccio C, Sabatino G, Medico E, et al. The MET oncogene drives a genetic programme linking cancer to haemostasis. Nature. 2005;434: 396-400.
61. Boccaccio C, Comoglio PM. A functional role for hemostasis in early cancer development. Cancer Res. 2005;65:8579-8582.
62. Bell WR, Starksen NF, Tong S, Porterfield JK. Trousseau's syndrome. Devastating coagulopathy in the absence of heparin. Am J Med. 1985; 79:423-430.
63. Krauth D, Holden A, Knapic N, Liepman M, Ansell J. Safety and efficacy of long-term oral anticoagulation in cancer patients. Cancer. 1987;59:983-985.
64. Walsh-McMonagle D, Green D. Low-molecular-weight heparin in the management of Trousseau's syndrome. Cancer. 1997;80:649-655.
65. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162: 1729-1735.
66. Levine M. Managing thromboembolic disease in the cancer patient: efficacy and safety of antithrombotic treatment options in patients with cancer. Cancer Treat Rev. 2002;28:145.
67. Alderman CP, McClure AF, Jersmann HP, Scott SD. Continuous subcutaneous heparin infusion for treatment of Trousseau's syndrome. Ann Pharmacother. 1995;29:710-713.
68. Hirsh J. Drug therapy: heparin. N Engl J Med. 1991;324:1565-1574.
69. Linhardt RJ, Gunay NS. Production and chemical processing of low molecular weight heparins. Semin Thromb Hemost. 1999;25(suppl 3):5-16.
70. Lindahl U. What else can 'heparin' do? Haemostasis. 1999;29(suppl 1):38-47.
71. Esko JD, Lindahl U. Molecular diversity of heparan sulfate. J Clin Invest. 2001;108:169-173.
72. Van Deerlin VM, Tollefsen DM. Molecular interactions between heparin cofactor II and thrombin. Semin Thromb Hemost. 1992;18:341-346.
73. Neese LL, Wolfe CA, Church FC. Contribution of basic residues of the D and H helices in heparin binding to protein C inhibitor. Arch Biochem Biophys. 1998;355:101-108.
74. Norgard-Sumnicht KE, Varki NM, Varki A. Calcium-dependent heparin-like ligands for L-selectin in nonlymphoid endothelial cells. Science. 1993;261:480-483.
75. Nelson RM, Cecconi O, Roberts WG, Aruffo A, Linhardt RJ, Bevilacqua MP. Heparin oligosaccharides bind L- and P-selectin and inhibit acute inflammation. Blood. 1993;82:3253-3258.
76. Norgard-Sumnicht KE, Varki A. Endothelial heparan sulfate proteoglycans that bind to L-selectin have glucosamine residues with unsubstituted amino groups. J Biol Chem. 1995;270:12012-12024.

77. Lorant DE, Topham MK, Whatley RE, et al. Inflammatory roles of P-selectin. J Clin Invest. 1993;92:559-570.
78. Furie B, Furie BC. P-selectin induction of tissue factor biosynthesis and expression. Haemostasis. 1996;26(suppl 1):60-65.
79. Alban S. Molecular weight-dependent influence of heparin on the form of tissue factor pathway inhibitor circulating in plasma. Semin Thromb Hemost. 2001;27:503-511.
80. Sandset PR, Bendz B, Hansen JB. Physiological function of tissue factor pathway inhibitor and interaction with heparins. Haemostasis. 2000; 30(suppl 2):48-56.
81. Ye ZY, Takano R, Hayashi K, et al. Structural requirements of human tissue factor pathway inhibitor (TFPI) and heparin for TFPI-heparin interaction. Thromb Res. 1998;89:263-270.
82. Hansen JB, Sandset PM, Huseby KR, Huseby NE, Bendz B. Differential effect of unfractionated heparin and low molecular weight heparin on intravascular tissue factor pathway inhibitor: evidence for a difference in antithrombotic action. Br J Haematol. 1998;101:638-646.
83. Abildgaard U. Tissue factor pathway inhibitor and heparin. Adv Exp Med Biol. 1992;313:199-204.
84. Ehrlich HJ, Keijer J, Preissner KT, Gebbink RK, Pannekoek H. Functional interaction of plasminogen activator inhibitor type 1 (PAI-1) and heparin. Biochemistry. 1991;30:1021-1028.
85. Liang JF, Li YT, Yang VC. The potential mechanism for the effect of heparin on tissue plasminogen activator-mediated plasminogen activation. Thromb Res. 2000;97:349-358.
86. Elsayed E, Becker RC. The impact of heparin compounds on cellular inflammatory responses: a construct for future investigation and pharmaceutical development. J Thromb Thrombolysis. 2003;15:11-18.
87. Capila I, Linhardt RJ. Heparin-protein interactions. Angew Chem Int Ed Engl. 2002;41:391-412.
88. Mulloy B, Linhardt RJ. Order out of complexity: protein structures that interact with heparin. Curr Opin Struct Biol. 2001;11:623-628.
89. Castelli R, Porro F, Tarsia P. The heparins and cancer: review of clinical trials and biological properties. Vasc Med. 2004;9:205-213.
90. Zacharski LR, Loynes JT. Low-molecular-weight heparin in oncology. Anticancer Res. 2003;23: 2789-2793.
91. McCart GM, Kayser SR. Therapeutic equivalency of low-molecular-weight heparins. Ann Pharmacother. 2002;36:1042-1057.
92. Bendz B, Andersen TO, Sandset PM. Dose-dependent release of endogenous tissue factor pathway inhibitor by different low molecular weight heparins. Blood Coagul Fibrinolysis. 2000; 11:343-348.
93. Hansen JB, Sandset PM. Differential effects of low molecular weight heparin and unfractionated heparin on circulating levels of antithrombin and tissue factor pathway inhibitor (TFPI): a possible mechanism for difference in therapeutic efficacy. Thromb Res. 1998;91:177-181.
94. Züger M, Biasiutti FD, Wuillemin WA, Furlan M, Lämmle B. Subcutaneous low-molecular-weight heparin for treatment of Trousseau's syndrome. Ann Hematol. 1997;75:165-167.
95. Ludwig RJ, Alban S, Bistrian R, et al. The ability of different forms of heparins to suppress P-selectin function in vitro correlates to their inhibitory capacity on bloodborne metastasis in vivo. Thromb Haemost. 2006;95:535-540.
96. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol. 2004;22:1944-1948.
97. Lee AY, Rickles FR, Julian JA, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol. 2005;23:2123-2129.
98. Mousa SA. Low-molecular-weight heparin in thrombosis and cancer. Semin Thromb Hemost. 2004;30(suppl 1):25-30.
99. Hoppensteadt D, Walenga JM, Fareed J, Bick RL. Heparin, low-molecular-weight heparins, and heparin pentasaccharide: basic and clinical differentiation. Hematol Oncol Clin North Am. 2003;17: 313-341.
100. Piccioli A, Lensing AW, Prins MH, et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. J Thromb Haemost. 2004;2:884-889.
101. Di Nisio M, Otten HM, Piccioli A, et al. Decision analysis for cancer screening in idiopathic venous thromboembolism. J Thromb Haemost. 2005;3: 2391-2396.
102. Prandoni P, Piccioli A. Thrombosis as a harbinger of cancer. Curr Opin Hematol. 2006;13:362-365.
103. Rickles FR, Levine MN. Venous thromboembolism in malignancy and malignancy in venous thromboembolism. Haemostasis. 1998;28(suppl 3):43-49.
104. Levine M, Rickles FR. Treatment of venous thromboembolism in cancer patients. Haemostasis. 1998;28(suppl 3):66-70.
105. Borsig L. Non-anticoagulant effects of heparin in carcinoma metastasis and Trousseau's syndrome. Pathophysiol Haemost Thromb. 2003; 33(suppl 1):64-66.
106. Miller GJ, Bauer KA, Howarth DJ, Cooper JA, Humphries SE, Rosenberg RD. Increased incidence of neoplasia of the digestive tract in men with persistent activation of the coagulant pathway. J Thromb Haemost. 2004;2:2107-2114.
107. Nierodzik M, Karpatkin S. Hypercoagulability preceding cancer. Does hypercoagulability awaken dormant tumor cells in the host? J Thromb Haemost. 2005;3:577-580.
108. Zacharski LR. Hypercoagulability preceding cancer. The iron hypothesis. J Thromb Haemost. 2005;3:585-588.