Thrombotic Microangiopathy Manifesting as Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome in the Cancer Patient

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ABSTRACT The complication of thrombotic thrombocytopenic purpura or hemolytic uremic syndrome (TTP/HUS) can occur in cancer patients. It is characterized by a microangiopathic hemolytic anemia, severe thrombocytopenia, and renal failure. Pulmonary manifestations, especially pulmonary edema, are a common observation. Neurologic changes are also frequently seen. The etiology is unknown at this time. It has been observed in many different types of cancer and is most commonly seen in gastric adenocarcinoma followed by carcinoma of the breast, colon, and small cell lung carcinoma. The hemolysis can be massive and is due to red cell fragmentation, as schistocytes are present in all the cases. Though immune complexes are present in the plasma, the antiglobulin (Coomb's) test is negative. Chemotherapeutic agents, especially mitomycin C, have been implicated as causative factors. There is a correlation of this complication with the cumulative dose. However, chemotherapy cannot account for all the cases as the syndrome can occur in untreated patients. It can be differentiated from disseminated intravascular coagulation by the absence of a coagulopathy. Management should consist of plasma exchange, use of a *Staphyloccus aureus* column (Prosorba), and control of hypertension. Because of the susceptibility to pulmonary edema, blood volume overloading should be avoided.

Keywords: Cancer, TTP/HUS, mitomycin C, plasmapheresis, microangiopathy

As the association between thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and cancer is well established,[1,2] it is fitting to update and review this entity in the present issue of *Seminars in Thrombosis and Hemostasis* devoted to the thrombophilic state of cancer. TTP/HUS should be regarded as a syndrome of severe thrombocytopenia and microangiopathic hemolytic anemia due to formation of widespread microthrombi composed mainly of platelets. Multiple forms of this syndrome are recognized, ranging from those in which the causative factor has been identified, such as in Shiga-toxin-induced TTP/HUS, to the more obscure idiopathic form. Though unfortunately the etiology of most forms of TTP/HUS is still an enigma, a number of contributing factors and much of the pathophysiologic process of their development are now beginning to unfold. In the case of the cancer-associated TTP/HUS, the toxicity of chemotherapeutic agents is implicated, but the role of the tumor cells may also be important. In this article, we will attempt to review the relevant recent literature and discuss the possible pathogenic mechanisms, then review the clinical features and treatment options of TTP/HUS associated with cancer.

Incidence

The true incidence of TTP/ HUS in cancer is uncertain, as in many case reports, the distinction with disseminated intravascular coagulation (DIC) is never made. Lohrman et al estimated an incidence of 5 to 6%,[3] but Brain et al reported that[4] five of 25 patients with de novo TTP/HUS had cancer, including three with gastric cancer. Among the cancers associated with TTP/HUS, adenocarcinoma predominates,[3,5-7] accounting for 88% of some series[7] with gastric adenocarcinoma being the most common type,[5,7] followed by breast cancer,[7-11] colorectal cancer,[12] small cell lung cancer,[13,14] squamous cancers,[15] thymoma,[16,17] and carcinoma of unknown primary origin. Chronic myelogenous leukemia[18] and Ka-

posi's sarcoma[19] have all been reported to be associated with TTP/HUS.

Clinical Features

Anemia, thrombocytopenia, and renal failure are always present[7] and are the common presenting manifestations. Though the anemia and thrombocytopenia may be confused with the marrow-suppressive effects of therapy or the cancer, it soon becomes apparent that these features are out of proportion to what is usually seen with chemotherapy for adenocarcinoma. In almost all of the cases, the presence of schistocytes is helpful in confirming the diagnosis.[7] The anemia and thrombocytopenia are usually severe, and reticulocytosis is often noted, with elevation of serum LDH levels indicating intravascular hemolysis.[20] The antiglobulin (Coomb's) test is negative, reflecting the lack of red cell autoantibodies, and the peripheral blood smear usually demonstrates abundant schistocytes. Jaundice (from the hemolysis), and nonfocal neurologic syndromes may occur. The neurologic manifestations of TTP/HUS associated with cancer are similar to those associated with idiopathic TTP/HUS,[2] and include headache, confusion,[2,21–23] hemiplegia or hemiparesis,[3,15,24] and coma.[25] Pulmonary manifestations are common and include pulmonary hypertension[26] and dyspnea. Noncardiogenic pulmonary edema is characteristic in this variety of TTP/HUS making it distinct from the other types. This is especially true in the late stages of the disease, when an ARDS-like picture or hemorrhage may develop as a terminal event,[27–29] or it may be related to complications of therapy,[30] such as intravenous immunoglobulin.[31] Another unusual feature is the presence of immune complexes in approximately 90% of the cases. The absence of coagulopathy with normal prothrombin time and normal partial thromboplastin time enables the differentiation from DIC.

Pathophysiology

The clinical manifestations of the TTP/HUS syndrome appear to be the result of an insult to the vascular endothelium, and the pathophysiology has been recently reviewed.[32,33] In TTP/HUS, hyaline thrombi are present in the small vessels, in capillaries, and arterioles, but not in venules.[34,35] A detailed analysis of the pathology of the vascular lesion[34,36,37] was common in the early literature. There is damage to endothelial cells which either is caused by or contributes to platelet agglutination, and then additional endothelial cell damage, vascular injury with a vicious cycle ending in progressive hemolysis, thrombocytopenia with renal, CNS, pulmonary failure, and death.[2,32,33,38] This process is probably not different in cancer-associated TTP/HUS. Recent studies by Nagaya and his group shed some light on this question.[39] They showed that levels of the cytokines TNFα, IL-1β, and IL-6 were elevated in patients with de novo

TTP/HUS and DIC but not in patients with mitomycin C-induced TTP/HUS. Similarly, von Willebrand factor (vWF) antigen and low molecular weight vWF multimers were reduced in DIC and de novo TTP/HUS, but not in the drug-induced syndrome. This despite the observation by others that the histopathology of small vessels in cancer-associated TTP/HUS and de novo TTP/HUS reveals similar findings[40,41] and that the red cell changes are indistinguishable in TTP/HUS (de-novo or cancer-associated) and a variety of other disorders, including malignant hypertension or renal cortical necrosis.[42] Recently, the role of the microvascular cell apoptosis[43] and the nitric oxide system[44,45] in the pathophysiology of TTP/HUS have been investigated.

The pulmonary changes that are associated with TTP/HUS may involve intimal proliferation in small pulmonary vessels. Tumor emboli were documented,[5,46] causing occlusion of the vascular lumen, though if this were the predominant mechanism more patients with tumor emboli should have microangiopathic hemolytic anemia.[47,48] Fibrin thrombi are also found,[40] though not always in association with tumor emboli. In some patients, the presence of intimal thickening with fibromuscular hyperplasia in the small pulmonary arteries suggests that the process in the lung may be a more chronic process.[45]

RELATIONSHIP TO DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

The pathologic lesions in cancer-associated TTP/HUS are difficult to distinguish from DIC, and defibrination has been described in an autopsy series.[49] The earliest demonstration of schistocytes in the blood of cancer patients came from Lohrman et al[3] but, the presence of red blood cell fragmentation in the blood of patients with metastatic cancer may indicate not only TTP/HUS but also DIC. Thus, it is important to distinguish on either laboratory or clinical grounds which pathophysiology is operative. There is a consumption of coagulation factors in DIC but not in TTP/HUS. The laboratory findings of coagulopathy are rarely seen in de-novo TTP/HUS but are present in DIC or may be present in cancer-associated TTP/HUS if there is concomitant low-grade DIC. Fibrin deposition occurs in tumor tissues,[50] and there was evidence of fibrin degradation in 75.4% of the 719 cancer patients studied.[51] Thus, DIC and TTP/HUS may coexist in cancer patients and may confuse the diagnosis. There may be vascular injury from chemotherapy or radiation, and tumor cells may invade vessels. Extensive vascular injury, or vasculitis,[52] can result in either DIC or TTP/HUS. It has been suggested that intravascular coagulation is not likely the initiating event in cancer-associated TTP/HUS[40] because the degree of coagulopathy and clotting factor consumption does not correlate with the amount of hemolysis. Further, evidence for DIC is pres-

ent in only about half of the patients with TTP/HUS.[40] Bull et al reported fine fibrin strands from 0.25 to 2μm in diameter, which sometimes contained tumor cells, red cells, white cells, but not platelets.[53,54]

Vascular hypertrophy and intimal hyperplasia can be seen in various forms of the TTP/HUS syndromes. These data suggest that the common pathway for vascular injury in these syndromes is not known, and support the idea that a generalized vasculopathy is present in cancer, in patients taking certain drugs, and after exposure to toxins[55-59] or organisms.[60,61]

The role of immune complexes in cancer-associated TTP/HUS has been studied,[41,62] and has led to immune modulation as a form of treatment. These include steroids and immunosuppressive drugs. Recently, the removal of immune complexes by immunoadsorption has been successfully used in patients with cancer chemotherapy-associated TTP/HUS.[63,64] Snyder et al[63] reported responses in 25 of 55 cases. Responders did better than nonresponders, with a 62% 1-year survival versus a 22% 1-year survival in nonresponders. Complement components C3 and C4 normalized, and immune complexes were cleared. Side effects included fever, chills, nausea, respiratory symptoms, and blood pressure changes. The mechanism of immune absorption therapy is not known, and though there is likely a clearing of immune complexes, other changes in the humoral and cellular immune systems[65-67] may occur. The exact role for this treatment modality remains uncertain, and further comparative trials are indicated.

Cancer Chemotherapy-associated TTP/HUS

Liu et al reported that renal toxicity caused by the anticancer drug mitomycin C was associated with microangiopathic hemolytic anemia and thrombocytopenia.[68] TTP/HUS has more recently been associated with many other anticancer drugs, including bleomycin, cisplatin, and gemcitabine.[69-72] Among those patients that had received mitomycin C, there was a trend to correlation with the cumulative dose.[7,73] Published reports in the literature showed that the cumulative doses exceed 40 mg/m2.[73,74] With chemotherapeutic agents other than mitomycin C, there was also an apparent dose relationship to the incidence of this complication. In a series of 581 patients with carcinoma of the breast receiving a high-dose regimen of cyclophosphamide, cisplatin, and carmustine, 2.6% developed TTP/HUS.[75]

It is often difficult to distinguish between cancer and cancer-chemotherapy-associated TTP/HUS. Murgo has reviewed the subject and has found features that separate these entities[40] though the distinction is far from easy to make. If the assertion that patients in remission likely suffer from chemotherapy-associated TTP/HUS is the discerning feature, it may not prove reliable as it is often difficult to achieve complete remissions from the metastatic adenocarcinomas that are seen in this syndrome.[1]

The incidence of renal and pulmonary manifestations may not help to distinguish the two, because most patients with metastatic cancer presenting today will have received some form of systemic chemotherapy. We have observed both renal and pulmonary failure in both. It is possible that the higher incidence of renal failure described by Murgo[40] and observed Snyder et al[63] is related to the added insult of potentially nephrotoxic drugs such as mitomycin C or cisplatin. We have seen responses with plasma exchange in both entities, whereas heparin therapy should be reserved for those patients who have documented acute DIC.

Elevated plasma vWF levels and arterial thrombosis in patients receiving cisplatin-based regimens have been described,[69] and a patient with a history of osteosarcoma who received four courses of single-agent cisplatin, then developed TTP/HUS, has been reported.[75] He was treated with hemodialysis, and the syndrome was resolved. The time interval from the initiation of chemotherapy in this patient was 10 months. The interval from the last dose to the development of the syndrome was 7 months, within the variable range of time of onset after drug exposure as described in the literature.

The antiestrogen tamoxifen contributed to the development of TTP/HUS in a patient with metastatic breast cancer who had previously been treated with a combination of mitomycin C, mitoxantrone, and methotrexate (3M). Autopsy findings were consistent with what would be expected after mitomycin C-associated TTP/HUS.[76] In a review of their experience with 94 patients who received 3M and tamoxifen, the authors found nine cases with TTP/HUS and suggested that there was an interaction between tamoxifen and one or more of the drugs in this regimen.[77] Other cancer chemotherapy agents reported to be associated with TTP/HUS include deoxycorfomycin,[78] methyl CCNU,[79] bleomycin,[69-71] and cytosine arabinoside, and daunomycin[80] in a patient with acute leukemia.

There are data that suggest that free radical injury may play a role in the pathogenesis of the endothelial cell injury which is associated with the clinical syndrome. The role of free radicals in this disorder of vascular endothelial cells deserves further study. Recently, Laurence et al reported that plasma from patients with acute TTP/HUS could induce apoptosis in cultured microvascular endothelial cells and that this was associated with the rapid induction of Fas (CD95) expression on these cells.[43,81]

We believe that the TTP/HUS syndromes are a significant cause of morbidity and mortality in the cancer patient, either because of the underlying disease or its treatment. Therapy with plasma exchange, immunoadsorption columns, or immunosuppressive drugs may be beneficial.[82] The TTP/HUS caused by other, noncancer-related drugs, should be considered in any patient who presents with clinical findings of anemia, thrombocytopenia, neurologic changes, or renal failure, and prompt therapy with plasma infusion and/or plasma exchange should be instituted.

The increased susceptibility to pulmonary edema in these patients requires meticulous care in limiting the volume of intravenous fluids. In some patients, the presence of hypertension may need special attention. The cause of the hypertension is not clear. Though the presence of a high plasma renal level suggests the use of an ACE inhibitor, this may not always be the case in other patients.[73]

Finally, new strategies for intervention should be based on a better understanding of vascular biology, and the occurrence in cancer patients may provide clues to the underlying mechanism.

REFERENCES

1. Gordon LI, Kwaan HC. Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 1997;34:140–147

2. Amorosi E, Ultmann J. Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine 1966;45:139–159

3. Lohrmann H-P, Adam W, Heymer B, et al. Microangiopathic hemolytic anemia in metastatic carcinoma: Report of eight cases. Ann Intern Med 1973;79:368–375

4. Brain M, Dacie J, Hourhaine DB. Microangiopathic hemolytic anemia: The possible role of vascular lesions in pathogenesis. Br J Haematol 1962;18:183–193

5. Antman K, Skarin A, Mayer R. Microangiopathic hemolytic anemia and cancer: A review. Medicine 1979;58:377–384

6. Brain M, Azzopardi J, Baker L, et al. Microangiopathic haemolytic anemia and mucin-forming adenocarcinoma. Br J Haematol 1970;18:183–193

7. Lesesne JB, Rothschild N, Reickson B, et al. Cancer associated hemolytic-uremic syndrome: Analysis of 85 cases from a national registry. J Clin Oncol 1989;7:781–789

8. van de Ven PJ, de Jong PC, Jansen GH, Blijham GH. Microscopic tumor embolisms in metastasized breast carcinoma. Ned Tijdschr Geneeskd 1997;141:536–540

9. Fisher DC, Sherrill GB, Hussein A, et al. Thrombotic microangiopathy as a complication of high-dose chemotherapy for breast cancer. Bone Marrow Transplant 1996;18:193–198

10. Rodenhuis SA, Westermann MJ, Holtkamo WJ, et al. Feasibility of multiple courses of high-dose cyclophosphamide, thiotepa, carboplantin for breast cancer or germ cell cancer. J Clin Oncol 1986;14:1473–1483

11. Cagnoni PJY, Nieto EJ, Shpall SI, et al. High-dose chemotherapy with autologous hemopoetic progenator-cell support as part of combined modality therapy in patients with inflammatory breast cancer. J Clin Oncol 1998;16:1661–1668

12. Robson MG, Abbs IC. Thrombotic thrombocytopenic purpura following hemicolectomy for colonic carcinoma. Nephrol Dial Transplant 1997;12:198–199

13. Canellos G. TTP and breast cancer. Case record of the Massachusetts General Hospital. N Engl J Med 1984;310:1728–1735

14. Davis SP, Rambotti F, Grignani F, et al. Microangiopathic hemolytic anemia and pulmonary small cell carcinoma. Ann Intern Med 1985;103:238 (letter)

15. Tapp E, Ralston A. Thrombotic microangiopathy associated with squamous carcinoma. Br Med J 1969;4:209–210

16. Rauch A, Tartaglia A, Kaufman B, et al. RBC fragmentation and thymoma. Arch Intern Med 1984;144:1280–1282

17. Hatama S, Kumagai H, Iwato K, Fujiwara M, Fujishima M. Thrombotic thrombocytopenic purpura accompanied by transient pure red cell aplasia and thymoma. Clin Nephrol 1998;49:193–197

18. Shammas F, Meyer P, Heikkila R, et al. Thrombotic microangiopathy in a patient with chronic myelogenous leukemia on hydroxyurea. Acta Haematol 1997;97:184–186

19. Avery RA, Denunzio TM, Craig DB. Thrombotic thrombocytopenic purpura associated with HIV and visceral Kaposi's sarcoma treated with plasmapheresis and chemotherapy. Am J Hematol 1998;58:148–149

20. Cohen JA, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenic purpura. J Clin Apheresis 1998;13:16–19

21. Stratford E, Tanbaka K. Microangiopathic hemolytic anemia in metastatic carcinoma. Arch Intern Med 1965;116:346–350

22. Guzzini F, Conti A, Esposito F. Simultaneous ischemic and hemorrhagic lesions of the brain detected by CT scan in a patient with thrombotic thrombocytopenic purpura. Haematologica 1998;83:280

23. Port JD, Beauchamp, Jr NJ. Reversible intracerebral pathologic entities mediated by vascular autoregulatory dysfunction. Radiographics 1998;18:353–367

24. Arboix A, Besses C. Cerebrovascular disease as the initial clinical presentation of haematological disorders. Eur Neurol 1997;37:207–211

25. Cohan M, Pitman G, Hoffman G. Hemolytic anemia, tumor cell emboli, and intravascular coagulation. Arch Pathol 1972;93:305–307

26. Monsuez JJ, Auperin I, Vittecoq D, Heshmati F. Pulmonary hypertension associated with thrombotic thrombocytopaenic purpura in AIDS patients. Eur Heart J 1997;18:1036–1037 [letter]

27. Bone R, Henry J, Petterson J, Amare M. Respiratory dysfunction in thrombotic thrombocytopenic purpura. Am J Med 1978;65:262–270

28. Sheldon R, Slaughter D. A syndrome of microangiopathic hemolytic anemia, renal impairmant, and pulmonary edema in chemotherapy-treated patients with adenocarcinoma. Cancer 1986;58:1428–1436

29. Torra R, Poch E, Torras A, Bombi J, Revert L. Pulmonary hemorrhage as a clinical manifestation of hemolytic-uremic syndrome associated with mitomycin C therapy. Chemotherapy 1993;39:453–456

30. Cantrell JE Jr., Phillips TM, Schein PS. Carcinoma-associated hemolytic–uremic syndrome: A complication of mitomycin C therapy. J Clin Oncol 1985;3:723–734

31. Suassuna JHR, da Costa MADL, Faria RA, Melichar AC. Noncardiogenic pulmonary edema triggered by intravenous immunoglobulin in cancer-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Nephron 1997;77:368–370

32. Moake JL. Studies on the pathophysiology of thrombotic thrombocytopenic purpura. Semin Hematol 1997;34:83–89

33. Moake JL, Chow TW. Thrombotic thrombocytopenic purpura: Understanding a disease no longer rare. J Am Med Sci 1998;316:10–19

34. Baehr G, Klemperer P, Schifrin A. An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles. Trans Assoc Am Physicians 1936;51:43–58

35. Gore I. Disseminated arteriolar and capillary platelet thrombosis: A morphologic study of its histogenesis. Am J Pathol 1950;26:155–175

36. Bernheim A. Widespread capillary and arteriolar platelet thrombi. Case report. J Mt Sinai Hosp 1943;10:287–291

37. Moschowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. Arch Intern Med 1925;36:89–93

38. Bukowski R. Thrombotic thrombocytopenic purpura: A review. Prog Hemost Thromb 1982;6:287–337

39. Nagaya S, Wada H, Oka KM, et al. Hemostatic abnormalities and increased vascular endothelial cell markers in patients with red

cell fragmentation syndrome induced by mitomycin C. Am J Hematol 1995;50:237–243

40. Murgo A. Thrombotic microangiopathy in the cancer patient including those induced by chemotherapeutic agents. Semin Hematol 1987;24:161–177

41. Korec S, Schein P, Smith F, et al. Treatment of cancer-associated hemolytic uremic syndrome with staphylococcal protein A immunoperfusion. J Clin Oncol 1986;4:210–215

42. Verwey J, Boven E, van der Meulen J, Pinedo HM. Recovery from mitomycin C induced hemolytic uremic syndrome: A case report. Cancer 1984;54:2878–2881

43. Laurence J, Mitra D. Apoptosis of microvascular endothelial cells in the pathophysiology of thrombotic thrombocytopenic purpura/sporadic hemolytic uremic syndrome. Semin Hematol 1997;34:98–105

44. Herlitz H, Petersson A. Sigstrom L, Wennmalm A, Westberg G. The arginine-nitric oxide pathway in thrombotic microangiopathy. Scand Urol Nephrol 1997;31:477–479

45. Jaradat ZW, Marquardt RR. L-Arginine as a therapeutic approach for the verotoxigenic Escherichia coli-induced hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Med Hypotheses 1997;49:277–280

46. Sato Y, Marutsuka K, Asada Y, et al. Case report, pulmonary tumor thrombotic microangiopathy. Pathol Int 1995;45:436–440

47. Gonzalez-Vitale J, Garcia-Bunuel R. Pulmonary tumor emboli in primary carcinoma of the lung. Cancer 1976;38:2105–2110

48. van de Ven PJ, de Jong PC, Jansen GH, Blijham GH. Microscopische tumorembolieen bij gemetastaseerd mammacarcinoom. Nederlands Tijdschrift Geneeskunde; 1997;141:536– 540

49. Seligsohn S, Weber H, Yoran C, et al. Microangiopathic hemolytic anemia and defibrination syndrome in metastatic carcinoma of the stomach. Israel Med 1968;4:69–75

50. McCardle R, Harper P, Aspar I, et al. Studies with Iodine[131] labeled antibody to human fibrinogen and neohydrin 203-Hq. Cancer 1967;20:865–870

51. Rickles F, Levine M, Edwards R, et al. Abnormalities in blood coagulation in patients with cancer. In Serniri G, Gensini G, Abbate R, Prisco D, eds. Thrombosis: An Update. Florence: Scientific Press; 1992;241–273

52. Miller A, Ryan PF, Dowling JP. Vasculitis and thrombotic thrombocytopenic purpura in a patient with limited scleroderma. J Rheumatol 1997;24:598–600

53. Bull B, Rubenberg M, Dacie J, et al. Microangiopathic haemolytic anemia: Mechanisms of red cell fragmentation; In-vitro studies. Br J Haematol 1968;14:643–652

54. Bull B, Kuhn I. The production of schistocytes by fibrin strands (a scanning electron microscope study). Blood 1970;35:104– 111

55. Boyce T, Swerdlow D, Griffin P. Escherichia coli 0157:H7 and the hemolytic-uremic syndrome. N Engl J Med 1995; 333:364–368

56. Martin D, MacDonald K, White K, Soler J, Osterholm M. The epidemiology and clinical aspects of the hemolytic uremic syndrome in Minnesota. N Engl J Med 1990;323:1161–1167

57. Easton L. Escherichia coli 0157: Occurrence, transmission and laboratory detection. Br J Biomed Sci 1997;54:57–64

58. Koutkia P, Mylonakis E, Flanigan T. Enterohemorrhagic Escherichia coli 0157:H7—an emerging pathogen [see comments]. Am Fam Physician 1997;56:853–856, 859–861

59. Takagi C, Naruse T. Verotoxin induced hemolytic uremic syndrome: Pathophysiology of neurological involvement. Nippon Rinsho 1997;55:731–735

60. Tarantolo SR, Landmark JD, Iwen PC, et al. Bartonella-like erythrocyte inclusions in thrombotic thrombocytopenic purpura [see comments]. Lancet 1997;350:1602 [letter]

61. Pawson R, Virchis A, Potter M, Prentice HG. Absence of Bartonella-like inclusions in microangiopathy after transplantation. Lancet 1998;351:831–832 [letter]

62. Zimmerman S, Smith F, Phillips T, Coffey R, Schein P. Gastric carcinoma and thrombotic thrombocytopenic purpura: Association with plasma immune complex concentrations. Br Med J 1982;284:1432

63. Snyder HJ, Mittleman A, Oral A, et al. Treatment of cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein A immunoadsorption of plasma. Cancer 1993;71:1882–1892

64. D'Souza RJ, Kwan JT, Hendry BM, Fallon M, Cunningham D. Successful outcome of treating hemolytic uremic syndrome associated with cancer chemotherapy with immunoadsorption. Clin Nephrol 1997;47:58–59

65. Snyder H, Balint JJ, Jones F. Modulation of immunity in patients with autoimmune disease and cancer treated by extracorporeal immunoadsorption with PROSORBA columns. Semin Hematol 1989;26(Suppl 1):31–41

66. Mehta R, Mittleman A, Ciavarella D, et al. The effect of autologous plasma immunoadsorption by staphylococcal protein A (SpA) columns (PROSORBA) on T-cell subsets and natural killer cells in patients with advanced cancer [abstract]. Clin Res 1986;34:501 (Abstr)

67. Oral A, Whiteside T, Guthrie T, Herberman R. Effects of extracorporeal immunoadsorption with Prosorba-staphylococcal protein A (SpA) column on parameters of cellular immunity. Blood 1989;74:145 (Abstr)

68. Liu K, Mittleman A, Sproue E, Elias E. Renal toxicity in man treated with mitomycin C. Cancer 1971;28:1314

69. Licciardello J, Moake J, Rudy C, Karp D, Hong W. Elevated plasma von Willebrand factor levels and arterial occlusive complications associated with cisplatin-based chemotherapy. Oncology 1985;42:296–300

70. Harrell R, Sibley R, Vogelzang N. Renal vascular lesions after chemotherapy with vinblastine, bleomycin, and cisplatinum. Am J Med 1982;73:429–433

71. Jackson A, Rose B, Graff LEA. Thrombotic microangiopathy and renal failure associated with antineoplastic chemotherapy. Ann Intern Med 1984;101:41–44

72. Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2′-difluordeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994;12:29–34

73. Wu DC, Liu JM, Chen YM, et al. Mitomycin-C induced hemolytic uremic syndrome: A case report and literature review. Jpn J Clin Oncol 1997;27:115–118

74. Spain RC. The case for mitomycin in non-small cell lung cancer. Oncology 1993;50(Suppl):35–50

75. Fisher DC, Sherrill GB, Hussein A, et al. Thrombotic microangiopathy as a complication of high-dose chemotherapy for breast cancer. Bone Marrow Trans 1996;18:193–198

76. Canoplat C, Pearson P, Jaffe N. Cisplatin-associated hemolytic-uremic syndrome. Cancer 1994;74:3059–3062

77. Montes A, Powles T, O'Brien M, et al. A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. Eur J Cancer 1993;29A:1854–1857

78. Sakai C, Takagi T, Wakatsuki S, Matsuzaki O. Hemolytic-uremic syndrome due to deoxycorfomycin: A report of the second case. J Intern Med 1995;34:593–596

79. Laffay D, Tubbs R, Valenzuela R, Hall P, McCormack L. Chronic glomerular microangiopathy and metastatic carcinoma. Hum Pathol 1979;10:433–438

80. Byrnes J, Baquerizo H, Gonzalez M. Thrombotic thrombocytopenic purpura subsequent to acute myelogenous leukemia chemotherapy. Am J Hematol 1986;21:299–304

81. Laurence J, Mitra D, Steiner M, Staiano-Coico L, Jaffe E. Plasma from patients with idiopathic and human immunodeficiency virus-associated thrombotic thrombocytopenic purpura induces apoptosis to microvascular endothelial cells. Blood 1996;87:3245–3254

82. Kwaan HC, Soff GA. Management of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 1997;34:159–166