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Drug-Induced Thrombotic Microangiopathy

Incidence, Prevention and Management

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Contents

Abstract

The term thrombotic microangiopathy (TMA) describes syndromes characterised by microangiopathic haemolytic anaemia, thrombocytopenia and variable signs of organ damage due to platelet thrombi in the microcirculation. In children, infections with *Shigella dysenteriae* type 1 or particular strains of *Escherichia coli* are the most common cause of TMA; in adults, a variety of underlying causes have been identified, such as bacterial and viral infections, bone marrow and organ transplantation, pregnancy, immune disorders and certain drugs. Although drug-induced TMA is a rare condition, it causes significant morbidity and mortality. Antineoplastic therapy may induce TMA. Most of the cases reported are associated with mitomycin. TMA has also been associated with cyclosporin, tacrolimus, muromonab-CD3 (OKT3) and other drugs such as interferon, anti-aggregating agents (ticlopidine, clopidogrel) and quinine. The early diagnosis of drug-induced TMA may be vital. Strict monitoring of renal function, urine and

blood abnormalities, and arterial pressure has to be performed in patients undergoing therapy with potentially toxic drugs. The drug must be discontinued immediately in the case of suspected TMA. Treatment modalities sometimes effective in other forms of TMA have been used empirically. Although plasma exchange therapy seems to be of value, the effectiveness of this approach has yet to be proved in multicentre, randomised clinical studies.

The term thrombotic microangiopathy (TMA) defines syndromes characterised by microangiopathic haemolytic anaemia and thrombocytopenia associated with variable signs of organ damage due to platelet thrombi in the microcirculation.[1] The different clinical manifestations of TMA are related to the different organ distribution of the lesions, which consist of intraluminal platelet thrombi and small vessel wall thickening with swelling and/or detachment of the endothelial cells from the basement membrane and accumulation of fluffy material in the subendothelial space.[1] These lead to haemolytic anaemia and thrombocytopenia through erythrocyte disruption and platelet consumption in the injured microcirculation. Some forms of TMA are dominated by renal impairment and are usually referred to as haemolytic uraemic syndrome (HUS); others show predominant central nervous system involvement and are referred to as thrombotic thrombocytopenic purpura.

Infections with *Shigella dysenteriae* type 1 or different strains of *Escherichia coli* (particularly O157:H7 serotype) are the most common cause of HUS, particularly in children.[2] The exotoxin (shigatoxin or Stx) produced by these bacteria causes diarrhoea, often bloody, and renal insufficiency through damage to the gastrointestinal and renal microvasculature. The outcome is usually good and the disease spontaneously resolves without renal sequelae in the majority of cases.[2]

In adults, the cause of TMA is often unknown, although many factors may be involved such as bacterial and viral infections, bone marrow and organ transplantation, pregnancy, immune disorders and certain drugs.[1] Neurological involvement is usually predominant, the prognosis is more severe and plasma exchange therapy is used to limit mortality and morbidity.

In this review we describe the incidence and clinical features of TMA, and discuss therapeutic and preventive options for TMA associated with certain drugs, in order to improve the knowledge about this rare but life-threatening complication of drug therapy. We also provide a general overview of the pathogenetic mechanisms of TMA in order to better understand those induced by drugs.

This paper is based on data derived from review and clinical research articles found in a Medline search of the English language literature up to 2000, using thrombotic microangiopathy, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, mitomycin, cyclosporin, tacrolimus (FK506), muromonab-CD3 (OKT3), interferon, ticlopidine, clopidogrel and quinine adverse effects as key words. Secondary references from the bibliographies of the initial articles were also evaluated, as were personal files.

1. Pathogenesis of Thrombotic Microangiopathy (TMA)

Injury to the endothelial cell is considered the central and probably inciting factor in the sequence of events leading to TMA.[3] This hypothesis is supported by the fact that most agents associated with the disease, including bacterial shigatoxins and endotoxins, viruses, antibodies, immunocomplexes and certain drugs, are toxic to the endothelium *in vitro*.[1] Since endothelial cells synthesise many substances involved in coagulation and fibrinolysis processes, such as prostacyclin, nitric oxide, von Willebrand Factor (vWF), thrombomodulin, tissue-type plasminogen activator inhibitor and protein S, the modification in the levels of these molecules that is reported in TMA could be responsible for the loss of physiological endothelium thromboresistance and for the subsequent

widespread platelet aggregation.[3] Many factors may play a role in endothelial injury. Shigatoxins damage human glomerular endothelial cells, either directly through inhibition of protein synthesis, or through up-regulation of cytokine production, polymorphonuclear leucocyte activation, and enhanced oxidant injury.[4] Bacteria-derived endotoxins may act synergistically with Stx, inducing the inflammatory reaction in target organs through the stimulation of local production of inflammatory mediators such as tumour necrosis factor α (TNF-α) or interleukins.[5-7]

Antibodies and immunocomplexes may also contribute to endothelial injury. Complement-dependent antibodies, cytotoxic for endothelial cells, have been detected in the serum and plasma of patients with TMA,[8-11] and immunoglobulin (Ig) G, IgM and complement are often found at the site of vascular lesions.[12] Moreover, TMA may be a complication of autoimmune diseases (particularly systemic lupus erythematosus),[13] acute vascular rejection, and antiphospholipid syndrome.[14] Since most of the proteins targeted by antiphospholipid antibodies are involved in regulation of the coagulation process, it is reasonable that they account for an increased thrombotic risk.

The interaction between leucocytes and damaged endothelial cells is extremely important for sustaining and amplifying microvascular injury.[7] Stx *in vitro* causes massive leucocyte adhesion and transmigration to endothelium by up-regulating endothelial expression of adhesive proteins and chemokines such as interleukin-8 and MCP-1.[15] Reactive oxygen species, released from adherent neutrophils, have a direct cytotoxic effect on vascular endothelium.

Upon the initial endothelial insult, platelet and leucocyte activation leads to activation and consumption of the complement system, with formation of the active C3b that reacts with any cell surface.[16] Increased release of complement cleavage products (including C3a and C5a) contributes to the microangiopathic process by stimulating neutrophil activation, phagocytic adhesion to vascular endothelium, or platelet aggregation, and by directly injuring the endothelium through enhanced production of the membrane attack complex, C5b-9.

In patients with TMA, vWF processing is also altered. In healthy individuals, vWF is formed in endothelial cells and megakaryocytes as ultra large (UL) multimers due to the polymerisation of a native subunit with apparent molecular mass of 225 kDa.[17] UL multimers are not normally present in circulation because they are reduced into smaller multimers soon after their secretion. Furlan et al.[18] and Tsai and Lia[19] have recently provided a major contribution to the understanding of vWF processing by describing a plasma metalloprotease that physiologically cleaves UL vWF multimers. In contrast to findings in healthy individuals, UL multimers of vWF were occasionally detected in the plasma of patients with TMA.[20-22] The fact that *in vitro* circulating UL multimers are capable of contributing to platelet aggregation more efficiently than normal multimers,[23] and that circulating UL multimers are present in both the acute and remission phases in patients with chronic relapsing TMA, was initially taken as evidence of a state of persistent endothelial perturbation.[24] However, recent findings showing that in a rare variant of von Willebrand disease (named Vicenza) circulating UL multimers were constantly detected,[25-26] and the patients never experienced thrombotic episodes but had a bleeding tendency, have challenged this hypothesis.

On the contrary, an increase in low molecular weight multimers and a decrease in high molecular weight multimers is constant in the acute phase of different forms of TMA and it might be the consequence of enhanced proteolytic fragmentation of the molecule.[18,27-29] Rising levels of shear stress increase vWF susceptibility to fragmentation, thus contributing to maintenance and further spread of microvascular thrombosis.[30]

Many cases of familial TMA have also been described, with the predominant features of HUS in two-thirds of patients.[31] Both autosomal recessive and autosomal dominant modes of inheritance have been recognised.[31-36] The genetic abnormality may involve the complement system. Extreme-

ly low levels of circulating C3, not derived from consumption, were found in a large series of familial cases as compared with controls.[37] Low C3 levels were also found in the patients' relatives, who had no present or past sign of the disease. Convincing data are now available that low C3 in HUS may derive from either lack[38,39] or altered function[40] of factor H, a regulatory protein that inhibits complement activation through the alternative pathway.

2. Drug-Induced TMA

2.1 Antineoplastic Drugs

TMA spontaneously arises in a few patients with advanced cancer and is also described as a complication of antineoplastic therapy. TMA complicates almost 6% of cases of metastatic carcinoma,[41] with gastric cancer alone accounting for about half of such cases. Prognosis of these patients is very poor and most of them die within a few weeks of diagnosis.

The association between TMA and antineoplastic therapy was first described by Liu et al.,[42] who reported the onset of renal injury, microangiopathic haemolytic anaemia and thrombocytopenia induced by mitomycin in 3 patients with metastatic carcinomas. Since then, syndromes with the characteristics of HUS, and less commonly thrombotic thrombocytopenic purpura, have been associated with many other antineoplastic drugs. Most of the reported cases of antineoplastic therapy-induced TMA are associated with mitomycin, which was the common denominator in 84 of 85 cases reported in 1987 from a national registry.[43] TMA has been described in 2 to 10% of patients with cancer treated with this drug.[44] Patients who develop mitomycin-induced TMA are usually well, and their cancer, usually an adenocarcinoma, is stable or in remission. Thus, they significantly differ from the very ill patients who develop TMA as a complication of advanced tumour.

2.1.1 Pathogenesis

The pathogenesis of mitomycin-induced TMA is not clearly understood. Mitomycin produces an experimental model of TMA on direct infusion into rat kidneys.[45] *In vitro*, mitomycin may directly damage vascular endothelial cells of the kidney and also inhibit prostacyclin production, thus promoting platelet aggregation and local intravascular coagulation. Circulating immunocomplexes, specific for tumour cell antigens, are seen in the majority of patients with mitomycin-induced TMA;[46] since they show an increased capacity to induce platelet aggregation *in vitro*, they might also favour platelet thrombus formation *in vivo*.

Mitomycin-induced TMA generally arises 4 to 8 weeks after the end of therapy but the onset may occur immediately after treatment or up to 9 months later.[44] At presentation, the most frequent objective findings are microangiopathic haemolytic anaemia, thrombocytopenia and renal failure. Oliguria is common but rarely progresses to anuria. Renal insufficiency is usually progressive and dialysis is required in almost one-third of patients. Urinalysis usually shows microscopic haematuria and mild proteinuria. In some cases, urine abnormalities may precede the onset of TMA. Neurological alterations occur less frequently. Systemic hypertension and noncardiogenic pulmonary oedema are common during the course of the disease. Conversely, fever is rare. The haematological findings show anaemia, usually severe, with haemoglobin levels less than 6.5 mg/dl in 40% of cases[47] and thrombocytopenia, with platelet counts below 60 000/mm^3 in most cases. Numerous fragmented red blood cells (schistocytes) with the typical aspect of burr or helmet cells are detected in the peripheral smear; elevated serum lactic dehydrogenase levels that reflect diffuse tissue ischaemia, reticulocytosis, low haptoglobin levels, circulating free haemoglobin, indirect hyperbilirubinaemia, and a negative Coombs' test are present.

Manifestations are dose related, rarely occurring in patients who receive doses lower than 30 mg/m^2 body surface area.[43] The case fatality rate is high, about 70%, and the median time to death is about 4 weeks. Most of the patients die of renal failure rather than cancer. Some patients surviving the acute phase may have a remission of the haemo-

lytic process and thrombocytopenia, but long term dialysis is often necessary. A few patients may have a complete recovery without recurrences.[48] Retrospective, nonrandomised data suggest that the addition of the antiestrogen tamoxifen to the chemotherapy combination of mitomycin, mitoxantrone and methotrexate (3M) may increase the risk of TMA.[49] Thus, the combination of these drugs should be avoided or carefully monitored.

TMA after chemotherapy with bleomycin and cisplatin is rare; most cases are attributed to the combination of the 2 drugs, supporting the idea that their association may be causative.[50,51] Other antineoplastic drugs whose association with TMA has been described include deoxycoformycin,[52] lomustine (CCNU),[53] daunorubicin,[54] cytarabine,[54] chlorozotocin,[55] zinostatin (neocarzinostatin),[56] gemcitabine[57] and estramustine phosphate sodium[58] (table I).

Table I. Drugs associated with the development of thrombotic microangiopathy

Antineoplastic agents
Mitomycin
Tamoxifen
Bleomycin
Cisplatin
Deoxycoformycin
Lomustine (CCNU)
Daunorubicin
Cytarabine
Chlorozotocin
Zinostatin (neocarzinostatin)
Gemcitabine
Estramustine phosphate sodium
Other drugs
Cyclosporin
Tacrolimus
Muromonab-CD3 (OKT3)
Interferon
Ticlopidine
Clopidogrel
Simvastatin
Quinine
Oral contraceptives
Penicillin
Penicillamine
Rifampicin (rifampin)
Metronidazole
Gemcitabine
Iodine

2.1.2 Secondary Prevention

Primary prevention of antineoplastic drug-induced TMA is extremely difficult because of the usefulness of these drugs, for which there is no substitute in most cases. Thus, secondary prevention is fundamental. It consists in early diagnosis of symptoms and signs, through strict monitoring of renal function, blood abnormalities and arterial pressure, to enable immediate discontinuation of the potentially toxic drug and provision of appropriate supportive care. Urinalysis is useful in the evaluation of haematuria and proteinuria; red blood cell and platelet counts and serum lactic dehydrogenase, reticulocyte and haptoglobin levels must be monitored as well as peripheral smears to evaluate the presence of schistocytes, the marker of the microangiopathic process. Treatment modalities that are sometimes effective in other forms of TMA, including corticosteroids, azathioprine, cyclophosphamide, vincristine, heparin, antiplatelet agents and epoprostenol (prostacyclin), have been attempted empirically. Corticosteroids, heparin and antiplatelet agents have been used without success in a small number of patients.[59] The possibility of preventing the onset of the syndrome through the use of corticosteroids in association with mitomycin needs to be confirmed.[60]

Since elevated levels of circulating immunocomplexes may play a role in this syndrome, the use of plasma therapy, removing these complexes, may be of value. In fact, this procedure usually normalises haematological abnormalities but rarely reverses renal insufficiency. Although exchange and infusion are equally effective when equivalent volumes of plasma are used,[61] plasma exchange should be considered as first choice therapy, since renal insufficiency and/or heart failure limit the amount of plasma that can be infused. The results of a few small randomised studies show that the use of cryosupernatant fraction (plasma from which a cryoprecipitate containing the largest plasma

vWF multimers, fibrinogen and fibronectin, has been removed) is as effective as fresh frozen plasma.[62]

The outlook for cancer-induced TMA seemed to improve when the efficacy of another procedure aimed to remove circulating immune complexes, immunoadsorption (the perfusion of autologous plasma over filters containing staphylococcal protein A covalently bound to polyacrylamide beads), was reported.[63] Staphylococcal protein A is a cell wall component of a pathogenic staphylococcus that nonspecifically binds the Fc portion of IgG. After immunoadsorption, plasma is then reinfused into the patient. In a pilot study, Korec et al.[63] reported the complete clearance of circulating immunocomplexes in 8 of 11 patients treated with this procedure, associated with haematological remission in 9 cases, stabilisation of renal function in 6 and long term remission in 7 cases. However, these encouraging results, which seemed to be better than those with conventional plasma exchange, have been only partially confirmed by a surveillance study in 55 patients with mitomycin-induced TMA.[46] Although patients who received immunoadsorption when cancer was in remission had a higher survival rate than historic control patients treated with combinations of corticosteroids, cytotoxic drugs, antiplatelet drugs, plasmapheresis, or other methods, a clinical response was achieved in only 25 patients and long term renal dialysis was not significantly reduced after this therapy.

Splenectomy may be considered in patients with disabling disease requiring frequent and prolonged courses of plasma therapy as well as bilateral nephrectomy in patients with severe renal impairment who are in imminent danger of death because of thrombocytopenia associated with severe, refractory hypertension and signs of hypertensive encephalopathy.[28] Transfusion of red blood cells should be administered only when deemed necessary, slowly and under strict control for the risk of an exacerbation of the syndrome (rapid worsening of haemolysis, renal function and pulmonary oedema).[64] Platelet transfusions should be avoided for the same reasons.

2.2 Cyclosporin

There are numerous reports of post-transplant TMA. The risk of TMA recurrence in patients who have received a cadaveric renal transplant and have a previous history of TMA is about 13%, irrespective of cyclosporin treatment, and is 30% in patients who have received a living kidney transplant.[65] The reasons for this difference are unknown, although it could be the consequence of familial forms of TMA which may have a higher risk of recurrence. The aetiology of familial HUS is probably multifactorial and the inherited defects, such as those concerning the complement system, might only represent a predisposing condition which increases the risk of the disease in combination to other intercurrent environmental or acquired factors. These forms of TMA are usually associated with a poor outcome, although plasma therapy in conjunction with supportive care may reduce mortality and morbidity.[66]

Cyclosporin-associated *de novo* TMA was first reported in a patient treated with cyclosporin to prevent graft-versus-host disease after allogeneic bone marrow transplantation.[67] Since then, TMA has been described after bone marrow, liver, heart and kidney transplant, and in patients with Behçets syndrome who were receiving long term cyclosporin.[66,68,69]

TMA in renal allograft recipients is most common in the first few weeks, when cyclosporin concentrations are highest, and has to be differentiated from humorally mediated rejection. These 2 events, which may be present at the same time, have similar clinical manifestations and histological changes; thus, in some cases a certain diagnosis cannot be established. Several mechanisms have been suggested to explain the pathogenesis of cyclosporin-induced TMA. Although direct endothelial damage may play an important role, cyclosporin may also increase platelet aggregation and thromboxane A_2 production; high cyclosporin concentrations correlate with enhanced thrombomodulin and vWF serum levels.[70] Moreover, cyclosporin stimulates the release of the potent vasoconstrictor endothelin and decreases prostacyclin

production.[71] Thus, a combination of endothelial toxicity and prothrombotic, antifibrinolytic and vasoconstrictive effects may favour the onset of TMA in some patients receiving cyclosporin therapy.

Prognosis of post-transplant TMA is generally poor. The graft survival rate following the episode of cyclosporin-associated TMA is about 43%.[72] Current treatment recommendations are the consequence of anecdotal experience, and multicentre, randomised clinical studies comparing various forms of therapy are necessary. Early diagnosis, reduction or discontinuation of cyclosporin, supportive care and plasma exchange may be the key to increasing graft survival.

2.3 Tacrolimus

Although there have been reports of successful conversion of patients with cyclosporin-associated TMA to tacrolimus therapy,[73,74] TMA has also been associated with tacrolimus. Since the first report in 1991,[75] 20 cases of tacrolimus-associated TMA have been described in the literature.[76] The reported incidence of tacrolimus-associated TMA ranges between 1 and 4.7%; it is more frequently diagnosed in the first year, although it may occur at any time of the post-transplantation phase. Trough concentrations of tacrolimus are not predictive of the development of TMA. Reduction or discontinuation of tacrolimus therapy and plasma exchange may be valid therapeutic procedures in tacrolimus-associated TMA. Loss of renal function and death occur rarely. The prognosis seems to be worse for patients who have received transplants other than kidney. Switching from tacrolimus to cyclosporin has been performed and may be associated with initial resolution of TMA, which may, however, recur later.[77-79]

2.4 Muromonab-CD3

TMA has also been associated with the administration of the anti-T cell monoclonal antibody muromonab-CD3.[80] This complication has been reported more commonly with high doses of muromonab-CD3 (10 mg/day) than with the currently recommended dosage of 5 mg/day. The alterations in the coagulation process induced by muromonab-CD3 may be mediated by the release of TNFα (and perhaps other cytokines) from circulating mononuclear cells.[81]

2.5 Other Drugs

There are other drugs whose association with TMA has been described. These include interferon-α,[82-85] interferon-β,[86] ticlopidine,[87-91] clopidogrel,[92] quinine,[93] simvastatin,[94] oral contraceptives,[95] penicillin,[96] penicillamine,[97] iodine,[98] rifampicin[99] and metronidazole.[100] For interferon, ticlopidine, clopidogrel and quinine, the association with TMA is well described; however, for other drugs, only isolated cases of TMA have been reported and the cause and effect association between the use of these drugs and the development of TMA is debated.

2.5.1 Interferon

TMA has been recently observed in patients treated with interferon for chronic myelogenous leukaemia, hairy cell leukaemia and hepatitis C.[82-86,101-107] How interferon may induce TMA has not been clarified. The mechanism is probably immunological; interferon may enhance cellular immunity[108] and stimulate the expression of HLA-DR antigens on glomerular and tubular cells with subsequent attack by activated lymphocytes.[109] Moreover, interferon-α may induce the production of autoantibodies[110] and the presence of antiphospholipids has also been reported in patients with interferon-associated TMA.[103] Finally, a direct nephrotoxic effect has been proposed.[111] In the 12 cases of interferon-associated TMA described in the literature, renal involvement was common and only 1 patient died of TMA. Prompt diagnosis, early discontinuation of the drug and supportive treatment contributed to improving the outcome. However, kidney prognosis was poor, since 5 patients needed long term dialysis and 2 experienced persistent renal failure; 4 patients had normal laboratory values. Some patients were given only supportive care, whereas others were treated with plasmapheresis and/or corticosteroids and vincristine.

However, on the basis of these few reported cases, it is not possible to evaluate the efficacy of a specific therapy in interferon-induced TMA.

2.5.2 Ticlopidine

Ticlopidine, an antiaggregating agent used for the treatment of intermittent claudication and prevention of stroke, and in patients with cardiac stents, has been rarely associated with the development of TMA. The estimated incidence of TMA following ticlopidine use is 1 case per 1600 to 5000.[87-91] A review of 60 cases showed that ticlopidine-induced TMA is characterised by predominant neurological abnormalities and occurred within 1 month of treatment in 80% of the cases.[89] The overall survival rate was 67%. Once ticlopidine therapy is stopped, treatment with plasma exchange may be associated with decreased mortality. However, clinicians have also to consider that ticlopidine may be beneficial in the treatment of TMA associated with other factors.[112]

2.5.3 Clopidogrel

Clopidogrel is a new antiaggregating agent which has a mechanism of action and chemical structure similar to those of ticlopidine. These agents block an adenosine diphosphate-binding site on platelets, which inhibits the expression of the glycoprotein IIb/IIIa receptor that binds fibrinogen and large vWF multimers. Clopidogrel has achieved widespread clinical use because of its generally favourable tolerability profile. However, Bennett et al.[92] recently described 11 cases of TMA that occurred during or soon after treatment with this drug was discontinued. Unlike the previously reported cases of ticlopidine-induced TMA, clopidogrel-induced TMA developed within 2 weeks of the initiation of therapy. As in ticlopidine-induced TMA, neurological alterations predominated. All patients were treated with plasma exchange and 2 of them required 20 or more exchanges before clinical improvement was achieved. Eight patients had complete resolution of TMA after the discontinuation of clopidogrel therapy, 2 had relapses that rapidly recovered after plasma exchange, and 1 patient died. Of interest is that half of the patients with clopidogrel-induced TMA were concomitantly treated with cholesterol-lowering drugs, and 1 patient had a recurrence during treatment with atorvastatin. Since 1 case of simvastatin-induced TMA is reported in the literature,[94] the possibility of adverse pharmacological interactions between cholesterol-lowering drugs and clopidogrel needs to be investigated. The mechanisms by which ticlopidine and clopidogrel may cause TMA are poorly understood. Ticlopidine is directly toxic to endothelial cells *in vitro*. Moreover, patients with ticlopidine-associated TMA may have a deficiency of vWF-cleaving protease activity in plasma comparable to that observed in idiopathic forms of TMA.

2.5.4 Quinine

Quinine-induced TMA is a rare, recently defined condition,[93] characterised by predominant renal impairment. It typically occurs in patients presensitised by prior exposure to quinine and rapidly follows reingestion of the drug. Quinine is generally used to treat muscle cramps but it is also contained in beverages (tonic water and bitter lemon drinks). Quinine-dependent antiplatelet, antierythrocyte and antigranulocyte antibodies have been involved in the pathogenesis of the disease. Despite the dramatic presenting symptoms and severe renal failure, the outcome is usually good if cessation of quinine and institution of plasma exchange are provided early enough.[113] Recovery of renal function is described in most cases. Avoidance of successive quinine use is necessary to prevent recurrences.

3. Conclusions

Drug-induced TMA is a rare condition that causes significant morbidity and mortality. It is important that clinicians become aware of this potential complication, since its early recognition may be vital. Strict monitoring of renal and haematological parameters and of blood pressure should be performed in patients undergoing therapy with potentially toxic drugs. Immediate discontinuation of the drug is necessary in the case of suspected TMA. Treatment for drug-induced TMA is not standardised and modalities that are sometimes effective

in other forms of TMA have been used empirically. Although plasma therapy seems to be of value, the effectiveness of this approach has yet to be proved in multicentre, randomised clinical studies.

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References

1. Remuzzi G, Ruggenenti P, Bertani T. Thrombotic microangiopathies. In: Tisher CC, Brenner BM, editors. Renal pathology. 2nd ed. Philadelphia (PA): JB Lippincott, 1994: 1154-84
2. Remuzzi G, Ruggenenti P. The hemolytic uremic syndrome. Kidney Int 1995; 47: 2-19
3. Zoja C, Remuzzi G. The pivotal role of the endothelial cell in the pathogenesis of HUS. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. New York (NY): Marcel Dekker, 1992: 389
4. Andreoli SP. The pathophysiology of the hemolytic uremic syndrome. Curr Opin Nephrol Hypertens 1999; 8: 459-64
5. Karpman D, Connell H, Svensson M, et al. The role of lipopolysaccharide and Shiga-like toxin in a mouse model of Escherichia coli 0157: H7 infection. J Infect Dis 1997; 175: 611-20
6. Fitzpatrick MM, Shah V, Trompeter RS, et al. Interleukin-8 and polymorphonuclear leukocyte activation in hemolytic uremic syndrome of childhood. Kidney Int 1992; 42: 951-6
7. Forsyth KD, Simpson AC, Fitzpatrick MM, et al. Neutrophil-mediated endothelial injury in hemolytic uremic syndrome. Lancet 1989; 2: 411-4
8. Burns ER, Zucker-Franklin D. Pathologic effects of plasma in patients with thrombotic thrombocytopenic purpura on platelets and cultured vascular endothelial cells. Blood 1982; 60: 1030
9. Neame PB. Immunologic and other factors in thrombotic thrombocytopenic purpura. Semin Thromb Hemost 1980; 6: 416
10. Koenig DW, Barley-Mahoney L, Daniel TO. A western blot assay detects autoantibodies to cryptic endothelial antigens in thrombotic microangiopathies. J Clin Immunol 1993; 13: 204
11. Leung YD, Moake JL, Havens PL, et al. Lytic anti-endothelial cell antibodies in hemolytic-uremic syndrome. Lancet 1988; 2: 183-6
12. Lian EC-Y. Pathogenesis of thrombotic thrombocytopenic purpura. Semin Hematol 1989; 24: 82
13. Musio F, Bohen EM, Yuan CM, et al. Review of thrombotic thrombocytopenic purpura in the setting of systemic lupus erythematosus. Semin Arthritis Rheum 1998; 28: 1-19
14. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine 1998; 77: 195-207
15. Zoja C, Morigi M, Remuzzi G, et al. Verotoxin-2 induces subendothelial leukocyte transmigration via upregulation of MCP-1 and IL-8 [abstract]. J Am Soc Nephrol 1998; 10: 595A-50
16. Winckstein JA, Sullivan KE, Colten HR. Biologic consequences of complement activation. In: Scriver CR, Beaudet AL, Sly WS, et al., editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, 1995: 3911
17. Wagner DD. Cell biology of von Willebrand factor. Annu Rev Cell Biol 1990; 6: 217-46
18. Furlan M, Robles R, Solenthaler M, et al. Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. Blood 1998; 91: 2839-46
19. Tsai HM, Lia ECY. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998; 339: 1585-94
20. Moake JL, McPherson PD. Abnormalities of von Willebrand factor multimers in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. Am J Med 1989; 87: 9N-15N
21. Rose PE, Enayat SM, Sunderland R, et al. Abnormalities of factor VIII related protein multimers in the haemolytic uraemic syndrome. Arch Dis Child 1984; 59: 1135-40
22. Galbusera M, Ruggenenti P, Remuzzi G, et al. Alpha1-antitrypsin therapy in a case of thrombotic thrombocytopenic purpura. Lancet 1995; 345: 224-5
23. Moake JL, Turner NA, Stathopoulos NA, et al. Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest 1986; 78: 1456-61
24. Moake JL. Moschcowitz, multimers, and metalloprotease. N Engl J Med 1998; 339: 1629-31
25. Mannucci PM, Lombardi R, Castaman G, et al. Von Willebrand disease 'Vicenza' with larger-than-normal (supranormal) von Willebrand factor multimers. Blood 1988; 71: 65
26. Zieger B, Budde U, Jessat U, et al. New families with von Willebrand disease type 2M (Vicenza). Thromb Res 1997; 87: 57
27. Galbusera M, Noris M, Remuzzi G, et al. Increased fragmentation of von Willebrand factor, due to abnormal cleavage of the subunit, parallels disease activity in recurrent hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and discloses predisposition in families. The Italian Registry of Familial and Recurrent HUS/TTP. Blood 1999; 94: 610-20
28. Remuzzi G, Galbusera M, Salvadori M, et al. Bilateral nephrectomy stopped disease progression in plasma-resistant hemolytic uremic syndrome with neurological signs and coma. Kidney Int 1996; 49: 282-6
29. Galbusera M, Benigni A, Remuzzi G, et al. Unrecognized pattern of von Willebrand factor abnormalities in hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. J Am Soc Nephrol 1999; 10: 1234-41
30. Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. Blood 1994; 83: 2171-9
31. Kaplan BS, Kaplan P. Hemolytic uremic syndrome in families. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. New York (NY): Marcel Dekker, 1992: 213
32. Franklin WA, Simon NM, Potter EW, et al. The hemolytic uremic syndrome. Arch Pathol 1972; 94: 230-40
33. Kirchner KA, Smith RM, Gockerman JP, et al. Hereditary thrombotic thrombocytopenic purpura: microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency occurring in consecutive generations. Nephron 1982; 30: 28-30
34. Bergstein J, Michael AJ, Kjellstrand C, et al. Hemolytic-uremic syndrome in adult sisters. Transplantation 1974; 17: 487-9
35. Pirson Y, Lefebvre C, Arnout C, et al. Hemolytic uremic syndrome in three adult siblings: a familial study and evolution. Clin Nephrol 1997; 28: 250-5

36. Carreras L, Romero R, Requesens C. Familial hypocomplementemic hemolytic uremic syndrome with HLA-A3, B7 haplotype. JAMA 1981; 245: 602-4
37. Noris M, Ruggenenti P, Remuzzi G, et al. Hypocomplementemia discloses genetic predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities. Italian registry of familial and recurrent hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. J Am Soc Nephrol 1999; 10: 281-93
38. Thompson RA, Winterborn MH. Hypocomplementemia due to a genetic deficiency of b1H globulin. Clin Exp Immunol 1981; 46: 110-9
39. Pichette V, Quérin S, Schürch W, et al. Familial hemolytic-uremic syndrome and homozygous factor H deficiency. Am J Kidney Dis 1994; 26: 936-41
40. Warwicker P, Goodship THJ, Donne RL, et al. Genetic studies into inherited and sporadic hemolytic uremic syndrome. Kidney Int 1998; 53: 836-44
41. Lohrmann HP, Adam W, Heymer B, et al. Microangiopathic hemolytic anemia in metastatic carcinoma: report of eight cases. Ann Intern Med 1973; 79: 368-75
42. Liu K, Mittleman A, Sproue E, et al. Renal toxicity in man treated with mitomycin C. Cancer 1971; 28: 1314-20
43. Lesesne JB, Rothschild N, Erickson B, et al. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. J Clin Oncol 1989; 7: 781-9
44. Murgo AJ. Cancer- and chemotherapy-associated thrombotic microangiopathy. In: Kaplan BS, Trompeter RS, Moake JL, editors. Hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. New York: Marcel Dekker, 1992: 271-97
45. Cattell V. Mitomycin-induced hemolytic uremic kidneys: an experimental model in rat. Am J Pathol 1985; 121: 88-95
46. SnyderWJr H, Mittelman 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: 1882-92
47. Bukowski RM. Thrombotic thrombocytopenic purpura. A review. In: Spaet TH, editor. Progress in hemostasis and thrombosis. New York (NY): Grune & Stratton, 1982: 287
48. Murgo AJ. Thrombotic microangiopathy in the cancer patient including those induced by chemotherapeutic agents. Semin Hematol 1987; 24: 161-77
49. 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: 1854-7
50. van der Heijden M, Ackland SP, Deveridge S. Haemolytic uraemic syndrome associated with bleomycin, epirubicin and cisplatin chemotherapy. A case report and review of the literature. Acta Oncol 1998; 37: 107-9
51. Palmisano J, Agraharkar M, Kaplan AA. Successful treatment of cisplatin-induced hemolytic uremic syndrome with therapeutic plasma exchange. Am J Kidney Dis 1998; 32: 314-7
52. Sakai C, Takagi T, Wakatsuki S, et al. Hemolytic-uremic syndrome due to deoxycoformycin: a report of the second case. Intern Med 1995; 34: 593-6
53. Laffay D, Tubbs E, Valenzuela R, et al. Chronic glomerular microangiopathy and metastatic carcinoma. Hum Pathol 1979; 10: 433-8
54. Byrnes JJ, Baquerizo H, Gonzalez M. Thrombotic thrombocytopenic purpura subsequent to acute myelogenous leukemia chemotherapy. Am J Hematol 1986; 21: 299-304
55. Kressel BR, Ryan KP, Duong AT, et al. Microangiopathic hemolytic anemia, thrombocytopenia and renal failure in patients treated for adenocarcinoma. Cancer 1981; 48: 1738-45
56. Cantrell JE, Phillips TM, Schein PS. Carcinoma associated hemolytic-uremic syndrome: a complication of mitomycin C chemotherapy. J Clin Oncol 1985; 3: 723-4
57. Nackaerts K, Daenen M, Vansteenkiste J, et al. Hemolytic-uremic syndrome caused by gemcitabine. Ann Oncol 1998; 9 (12): 1355
58. Tassinari T, Sartori S, Panzini I, et al. Hemolytic uremic syndrome during therapy with estramustine phosphate for advanced prostatic cancer. Oncology 1999; 56: 112-3
59. Chow S, Roscoe J, Cattran DC. Plasmapheresis and antiplatelet agents in the treatment of the hemolytic uremic syndrome secondary to mitomycin. Am J Kidney Dis 1986; 7: 407-12
60. Blanco R, Griffin J, Radice P. Mitomycin-C pulmonary toxicity protective measures. Proc Am Soc Clin Oncol 1986; 5: 48
61. Novitzky N, Jacobs P, Rosenstrauch W. The treatment of thrombotic thrombocytopenic purpura: plasma infusion or exchange? Br J Haematol 1994; 87: 317-20
62. North American TTP Group, Ziegler Z, Gryn JF, et al. Cryopoor plasma does not improve early response in primary adult thrombotic thrombocytopenic purpura (TTP) [abstract]. Blood 1998; 92: 707a
63. Korec S, Schein PS, Smith FP. Treatment of cancer-associated hemolytic-uremic syndrome with staphylococcal protein A immunoperfusion. J Clin Oncol 1986; 4: 210-5
64. Bruntsch U, Groos G, Tigges FJ, et al. Microangiopathic hemolytic anemia, a frequent complication of mitomycin therapy in cancer patients. Eur J Cancer Clin Oncol 1984; 20: 905-9
65. Ruggenenti P, Remuzzi G. The pathophysiology and management of thrombotic thrombocytopenic purpura. Eur J Haematol 1996; 56: 191-207
66. Agarwal A, Mauer SM, Matas AJ, et al. Recurrent hemolytic uremic syndrome in an adult renal allograft recipient: current concepts and management. J Am Soc Nephrol 1995; 6: 1160-9
67. Powles RL, Clink HM, Spence D, et al. Cyclosporin A to prevent graft-versus-host disease in man after allogeneic bone marrow transplantation. Lancet 1980; I: 327-9
68. Remuzzi G, Bertani T. Renal vascular and thrombotic effects of cyclosporine. Am J Kidney Dis 1989; 13: 261-72
69. Pettitt AR, Clark RE. Thrombotic microangiopathy following bone marrow transplantation. Bone Marrow Transplant 1994; 14: 495-504
70. Schriber JR, Herzig GP. Transplantation-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 1997; 34: 126-33
71. Bunchman TE, Brookshire CA. Cyclosporine-induced synthesis of endothelin by cultured human endothelial cells. J Clin Invest 1991; 88: 310-4
72. Katznelson S, Wilkinson A, Rosenthal TR, et al. Cyclosporine-induced hemolytic uremic syndrome: factors that obscure its diagnosis. Transplantation Proc 1994; 26: 2608-9
73. Daufman DB, Kaplan B, Kanwar YS, et al. The successful use of tacrolimus (FK506) in a pancreas/kidney transplant recipient with recurrent cyclosporine-associated hemolytic uremic syndrome. Transplantation 1995; 59: 1737-9
74. Abdalla AH, Al-Sulaiman MH, Al-Khader AA. FK506 as an alternative in cyclosporine-induced hemolytic uremic syndrome in a kidney transplant recipient. Transplant Int 1994; 7: 382-4
75. Schmidt R, Venkat K, Dumler F. Hemolytic-uremic syndrome in a renal transplant recipient on FK506 immunosuppression. Transplant Proc 1991; 23: 3156
76. Trimarchi HM, Truong LD, Brennan S, et al. FK506-associated thrombotic microangiopathy. Transplantation 1999; 67: 539-44

77. Mihatsch M, Ryffel B, Gudat F, et al. Cyclosporine nephropathy. In: Tisher CC, Brenner BM, editors. Renal pathology with clinical and functional correlations. Philadelphia (PA): JB Lippincott, 1989: 1570
78. Scantlebury V, Shapiro R, Mc Cauley J, et al. Renal transplantation under cyclosporine and FK506 for hemolytic uremic syndrome. Transplant Proc 1995; 27: 842
79. Myers JN, Shabshab SF, Burton NA, et al. Successful use of cyclosporine in a lung transplant recipient with tacrolimus-associated hemolytic uremic syndrome. J Heart Lung Transplantation 1999; 18 (10): 1024-6
80. Abramowicz D, Pradier D, Marchant A, et al. Induction of thromboses within renal grafts by high-dose prophylactic OKT3. Lancet 1992; 339: 777-8
81. Pradier D, Marchant A, Abramowicz D, et al. Procoagulant effect of the OKT3 monoclonal antibody: involvement of tumor necrosis factor. Kidney Int 1992; 42: 1124
82. Lacotte L, Thierry A, Delwail V, et al. Thrombotic thrombocytopenic purpura during interferon alpha treatment for chronic myelogenous leukemia. Acta Haematol 2000; 102: 160-2
83. Vacher-Coponat H, Opris A, Daniel L, et al. Thrombotic microangiopathy in a patient with chronic myelocytic leukaemia treated with alpha-interferon. Nephrol Dial Transplant 1999; 14: 2469-71
84. Ravandi-Kashani F, Cortes J, Talpaz M, et al. Thrombotic microangiopathy associated with interferon therapy for patients with chronic myelogenous leukemia: coincidence or true side effect? Cancer 1999; 85: 2583-8
85. Rachmani R, Avigdor A, Youkla M, et al. Thrombotic thrombocytopenic purpura complicating chronic myelogenous leukemia treated with interferon-alpha. A report of two successfully treated patients. Acta Haematol 1998; 100: 204-6
86. Ubara Y, Hara S, Takedatu H, et al. Hemolytic uremic syndrome associated with beta-interferon therapy for chronic hepatitis C [letter]. Nephron 1998; 80: 107-8
87. Page Y, Tardy B, Zeni F, et al. Thrombotic thrombocytopenic purpura related to ticlopidine. Lancet 1991; 337: 774-6
88. Leavey SF, Weinberg J. Thrombotic thrombocytopenic purpura associated with ticlopidine therapy. J Am Soc Nephrol 1997; 8: 689-93
89. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. Ann Intern Med 1998; 128: 541-4
90. Bennett CL, Kiss JE, Weinberg PD, et al. Thrombotic thrombocytopenic purpura after stenting and ticlopidine. Lancet 1998; 352: 1036-7
91. Chen DK, Kim JS, Sutton DM. Thrombotic thrombocytopenic purpura associated with ticlopidine use. A report of 3 cases and review of the literature. Arch Intern Med 1999; 159: 311-4
92. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342: 1773-7
93. McDonald SP, Shanahan EM, Thomas AC, et al. Quinine-induced hemolytic uremic syndrome. Clin Nephrol 1997; 47: 397-400
94. McCarthy LJ, Porcu P, Fausel CA, et al. Thrombotic thrombocytopenic purpura and simvastatin. Lancet 1998; 352: 1284-5
95. Schoolwerth A, Sandler R, Klahr S, et al. Postpartum nephrosclerosis in women taking oral contraceptives. Arch Intern Med 1976; 136: 178-85
96. Parker C, Barnett D. Microangiopathic hemolysis and thrombocytopenia related to penicillin drugs. Arch Intern Med 1971; 127: 174-7
97. Trice J, Pinale R, Plitman G. Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. Arch Intern Med 1983; 143: 1487-8
98. Ehrich W, Seifter J. Thrombotic thrombocytopenic purpura caused by iodine. Arch Pathol 1949; 47: 446-9
99. Fahal I, Williams P, Clark R, et al. Thrombotic thrombocytopenic purpura due to rifampicin. BMJ 1992; 304: 882
100. Lakkis FG, Campbell OC, Badr KF. Microvascular diseases of the kidney. In: Brenner BM, editor. The kidney, 5th ed. Philadelphia (PA): Saunders, 1996: 1712-7
101. Iyoda K, Kato M, Nakagawa T, et al. Thrombotic thrombocytopenic purpura developed suddenly during interferon treatment for chronic hepatitis C. J Gastroenterol 1998; 33: 588-92
102. Honda K, Ando A, Endo M, et al. Thrombotic microangiopathy associated with alpha-interferon therapy for chronic myelocytic leukemia. Am J Kidney Dis 1997; 30: 123-30
103. Piette JC, Papo T. Potential role for antiphospholipid antibodies in renal thrombotic microangiopathy induced by interferon-alpha [letter]. Nephrol Dial Transplant 1995; 10: 1781
104. Jadoul M, Piessevaux H, Ferrant A, et al. Renal thrombotic microangiopathy in patients with chronic myelogenous leukaemia treated with interferon-alpha 2b. Nephrol Dial Transplant 1995; 10: 111-3
105. Schlaifer D, Dumazer P, Spenatto N, et al. Hemolytic-uremic syndrome in a patient with chronic myelogenous leukemia treated with interferon alpha [letter]. Am J Hematol 1994; 47: 254-5
106. Harvey M, Rosenfeld D, Davies D, et al. Recombinant interferon alpha and hemolytic uremic syndrome: cause or coincidence? [letter]. Am J Hematol 1994; 46: 152-3
107. Stratta P, Canavese C, Dogliani M, et al. Hemolytic-uremic syndrome during recombinant alpha-interferon treatment for hairy cell leukemia. Ren Fail 1993; 15: 559-61
108. Averbuch SD, Austin III HA, Sherwin SA, et al. Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. N Engl J Med 1984; 310: 32-4
109. Kramer P, Ten Kate FWJ, Bijnen AB. Recombinant leukocyte interferon α induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. Lancet 1984; I: 989-90
110. Ronnblom LE, Alm GV, Oberg KE. Autoimmunity after alpha-interferon therapy for malignant carotid tumors. Ann Intern Med 1991; 115: 178-83
111. Ault BH, Stapleton FB, Gaber L, et al. Acute renal failure during therapy with recombinant human gamma interferon. N Engl Med J 1988; 319: 1397-400
112. Vianelli N, Catani L, Belmonte MM, et al. Ticlopidine in the treatment of thrombotic thrombocytopenic purpura: report of two cases. Haematology 1990; 75: 274-7
113. Gottschall JL, Neahring B, McFarland JG, et al. Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. Am J Hematol 1994; 47: 283-9

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