Haemolytic uraemic syndrome following bone marrow transplantation. Case report and review of the literature

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Abstract Thrombotic microangiopathy (TMA) can be a late complication of bone marrow transplantation (BMT). A patient is described in whom the haemolytic uraemic syndrome developed 10 months after BMT and who died of E.coli sepsis while on maintenance haemodialysis. The literature is reviewed, regarding clinical presentation, incidence, pathogenesis and therapy. TMA can be observed, after an interval of 3–12 months, in about 6–26% of patients following BMT. Reported cases vary considerably in clinical severity, from mild presentations to severe TMA with high mortality rates despite intensive therapy. Important pathogenetic roles are ascribed to the conditioning total body irradiation and the use of cyclosporin A, but other factors may be involved as well. Next to supportive therapy, plasma exchange and the use of ACE inhibitors may be of value in treating BMT-associated TMA.

Key words: bone marrow transplantation; cyclosporin A; haemolytic uraemic syndrome; thrombotic microangiopathy; thrombotic thrombocytopenic purpura; total body irradiation

Introduction

The haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are closely related components of a clinical syndrome designated as thrombotic microangiopathy (TMA), characterized by the presence of microthrombi (consisting of platelets and fibrin) in arterioles and capillaries. TMA can be observed in many different clinical conditions, and displays the following characteristics: (a) haemolytic anaemia due to mechanical trauma to erythrocytes, as indicated by the presence of fragmented erythrocytes, so-called schistocytes, in peripheral blood and negative Coombs’ tests; (b) thrombocytopenia, possibly due to both increased local consumption and increased degradation; (c) thrombotic lesions in various organs resulting in a clinical spectrum varying from renal failure and hypertension (‘HUS’) to dysfunction of multiple organs including neurological signs and symptoms (‘TTP’).

The key factor in the pathogenesis of TMA appears to be a dysregulation in the normal interaction of vascular endothelium and platelets, resulting from diverse endothelial derangements such as defects in prostacyclin activity, plasminogen activity or von Willebrand factor multimeric structure, or from enhanced platelet aggregation caused by the presence of stimulatory factors or the absence of inhibitory factors in the plasma [1]. The various defects may be genetic in nature or acquired. Accordingly, numerous possible causes of TMA have been identified, including idiopathic and hereditary forms of HUS and TTP, and TMA secondary to infections (e.g. with verotoxin-producing strains of E.coli), systemic vascular disease (such as SLE and systemic sclerosis), malignant hypertension, TMA associated with pregnancy and the postpartum period, disseminated malignancies, and drugs such as oral contraceptives and mitomycin-C [2,3].

In the past decade, bone marrow transplantation (BMT) has been added to the long list of conditions associated with TMA. In the present paper, a case of TMA following BMT is reported, and relevant literature regarding clinical presentation and pathogenesis is reviewed.

Case report

A 45-year-old woman was referred to our hospital in July 1993 for bone marrow transplantation (BMT). In April 1993, thrombocytosis (733 x 10⁹/l) and leukocytosis (17.7 x 10⁹/l) were observed in the analysis of peripheral cytology. Bone marrow examination revealed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) with an additional inversion of chromosome 17. Treatment with hydroxyurea was instituted. Because of the unfavourable prognosis associated with the chromosomal abnormalities, she was considered as a candidate for BMT. After conditioning chemotherapy (cyclophosphamide
60 mg/kg on days -6 and -5) and total body irradiation with 5 MV photons (9 Gy on day 0), allogeneic bone marrow transplantation (alloBMT) was performed in September 1993. The donor was an HLA-identical sister, and the graft was T-cell depleted by in vitro incubation with Campath-1G (10 mg). The transplantation was complicated by herpes simplex stomatitis and unilateral peripheral facial nerve paralysis for which treatment with acyclovir was instituted. One month later, graft versus host disease (GvHD) of the skin developed (grade 1), which was treated with topical corticosteroids. In November 1993 the patient was readmitted because of pancytopenia (Figure 1) and retinitis, both due to CMV infection, which was successfully treated with ganciclovir. By January 1994, haemoglobin had increased to 7.6 mmol/l, WBC was 4.3 x 10^9/l and platelets were 122 x 10^9/l. In May 1994 she developed a Coombs-negative haemolytic anaemia (Hb 6.6 mmol/l), leukopenia (WBC 3.0 x 10^9/l) and thrombocytopenia (25 x 10^9/l) (Figure 1). No viral infection (CMV, EBV, parvovirus B19) could be detected. Bone marrow examination revealed adequate erythropoiesis and megakaryopoiesis, and no evidence for recurrence of CML. Cytogenetic analysis was negative for Philadelphia chromosome. However, blood group typing showed all red cells to be acceptor type, indicating recovery of autologous erythropoiesis. As the pancytopenia was presumed to be an immune phenomenon associated with recovery of autologous haematopoiesis, treatment with prednisone (60 mg daily) was instituted. However, anaemia and thrombocytopenia did not improve and RBC transfusions became necessary.

In July 1994 the patient was hospitalized because of Haemophilus influenzae pneumonia. At that time, laboratory investigation disclosed the presence of Coombs-negative haemolytic anaemia (Hb 4.4 mmol/l, LDH 600 U/l, and markedly decreased haptoglobin levels) and thrombocytopenia with increased schistocyte counts (4–6%) in peripheral blood smears. Also, serum creatinine had increased from 70 to 200 μmol/l, associated with the development of hypertension (180/105 mmHg), microscopic haematuria and proteinuria (2 g/24 h). A diagnosis of haemolytic uraemic syndrome (HUS) was made. Treatment was instituted with enalapril (20 mg daily), plasmapheresis (30 ml/kg, initially daily, after 2 weeks thrice weekly) and vincristine (2 mg weekly), while prednisone was continued. With this regimen, hypertension was successfully controlled and haematological parameters showed some improvement (Figure 1). Yet renal failure did not respond to therapy; plasmapheresis and vincristine were discontinued after 1 month. In September 1994, signs of haemolysis recurred, together with a further increase in serum creatinine, development of oliguria and worsening of hypertension. Despite a second trial of plasmapheresis, end-stage renal failure developed and chronic intermittent haemodialysis was instituted in October 1994. In January 1995 the patient was readmitted in septic shock, which proved to be rapidly fatal. Blood cultures grew E.coli. Post-mortem examination of the kidneys disclosed widespread and severe arteriosclerosis; no microthrombi were seen.

**Discussion**

In the above case, a diagnosis of haemolytic uraemic syndrome (HUS) was made on the basis of clinical features and laboratory findings. Renal biopsy was not performed in the presence of thrombocytopenia. Post-mortem examination of the kidneys revealed widespread arteriolar thickening and glomerular ischaemia/fibrosis as sequelae of arteriolar thrombotic microangiopathy [4,5].

**Clinical characteristics of BMT-associated TMA**

Since its first description in 1978 [6], numerous cases of BMT-associated TMA have been reported (cf Table 1), most often in the haematological literature. Signs of TMA consisted of de novo thrombocytopenia and anaemia (or an increase in transfusion requirements in this group of patients) along with increases in lactate dehydrogenase (LDH) and decreased haptoglobin levels. Direct and indirect Coombs’ tests were negative and schistocytes were present in blood smears. Renal involvement was evidenced by rises in serum creatinine levels, accompanied by microscopic haematuria and mild proteinuria. Hypertension was frequently present, and often required the use of multiple anti-hypertensive drugs. Most cases of TMA originated in patients who had recovered from BMT and who were in a stable clinical condition with remission of the original haematological disease. Some patients displayed TMA within 1 month following BMT, whereas
intensive therapy including plasmapheresis. Death was seen with profound renal failure, often necessitating cases only mild renal failure occurred, in which mortality was high (up to 88%) despite renal replacement therapy, and severe hypertension, noted, sometimes accompanied by mesangial cell proliferation (cf Table 1). On the one hand [14,19], in many and arteriolosclerosis, often also with deposition of thrombi. On the other hand [5,15,16,18,20], cases were played, in varying degrees, oedema of the intima and proliferation. The arterioles and interlobular arteries displayed, leading to fibroplasia. The arterioles and interlobular arteries displayed, leading to fibroplasia.

The nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was seen, from biopsies or post-mortem material, were identical to the basement membrane. Focal thickening of the mesangium was noted, sometimes accompanied by mesangial cell proliferation, leading to fibroplasia and arteriolosclerosis, often also with deposition of electron-lucent material was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was observed; the exact nature of this material is not clear.

Morphological findings in renal tissue, obtained from biopsies or post-mortem material, were identical to those observed in other forms of TMA [5,9,12,15,18,23,24]. Glomerular changes consisted of swelling of endothelial cells, often with detachment from the basement membrane. Focal thickening of the basement membrane with subendothelial deposits of electron-lucent material was observed; the exact nature of this material is not clear. Glomerular capillary lumina were narrowed and contained microthrombi. In many cases oedema of the mesangium was noted, sometimes accompanied by mesangial cell proliferation. The arterioles and interlobular arteries displayed, in varying degrees, oedema of the intima and myointimal cell proliferation, leading to fibroplasia and arteriolosclerosis, often also with deposition of thrombi.

Of note in the different descriptions of BMT-associated TMA is the striking variability in clinical presentation (cf Table 1). On the one hand [14,19], in many cases only mild renal failure occurred, in which mortality, even in the absence of any specific therapy, was low. On the other hand [5,15,16,18,20], cases were seen with profound renal failure, often necessitating renal replacement therapy, and severe hypertension, sometimes accompanied by neurological symptoms. In these cases, mortality was high (up to 88%) despite intensive therapy including plasmapheresis. Death was most often the result of infectious complications, in some cases related to dialysis procedures, or because of extensive damage of multiple organs ("TTP-like" disease). In survivors, haematological parameters generally displayed gradual improvement.

Incidence of BMT-associated TMA
Deterioration of renal function following BMT is a frequent occurrence [9,22,25,26], which in a number of cases can be ascribed to intercurrent systemic infections or the use of nephrotoxic drugs such as aminoglycoside antibiotics. On the basis of published data it is difficult to obtain a correct estimation of the incidence of TMA following BMT. Thus most reports are based on retrospective analyses of data. In many instances it is not clear whether collection of data has been carried out in sufficient detail to detect all cases of TMA. Anaemia and thrombocytopenia are often present following BMT, and cases of BMT-associated TMA might have gone undetected when serum LDH and the presence of schistocytes were not systematically investigated in all patients. Also some cases have been described in which deterioration of renal function and renal biopsy findings of TMA were not associated with haemolytic anaemia or thrombocytopenia [5,23,24,26]. In general, TMA following BMT appears not to be an infrequent event (cf Table 2). Five studies prospectively investigated the occurrence of BMT-associated TMA, i.e. laboratory findings of microangiopathic haemolytic anaemia and decrease in renal function. In four of these [10,19,22,24], the incidence was found to be 6–26%; in most cases the clinical presentation and

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* data in children.
Auto/allo, autologous versus allogeneic BMT. CsA, cyclosporin A; CY, cyclophosphamide; Ara-C, cytosine-arabinoside; daun, daunorubicin; bus, busulphan; eto, etoposide. ND, no data available.
degree of renal failure were relatively mild. In the fifth study [16] a very high incidence of BMT-associated TMA was noted: 49 of 66 patients had laboratory evidence of TMA and deterioration of renal function; in 10 patients severe renal insufficiency, often with neurological findings, was present. All patients in the latter study used CsA. Whether this fact contributed to the high incidence and severity of clinical signs remains speculative.

Pathogenesis of BMT-associated TMA

The diversity in clinical severity probably reflects the heterogeneity in the pathogenesis of BMT-associated TMA. As in other forms of TMA [4,27], it is likely that severe renal failure and hypertension are associated with more pronounced arteriolar and arterial damage, while in cases with mainly glomerular capillary pathology a milder clinical presentation would be present [15]. In this respect it is of interest, albeit speculative, that when comparing the different clinical descriptions one gets the impression that more severe cases were observed among patients who received cyclosporin A (see Table 1): CsA is known to induce changes at the arteriolar level. In the pathogenesis of TMA, endothelial damage and local platelet aggregation play important roles. In BMT various circumstances are present which have the potential of inducing such changes, such as infection by cytomegalovirus (CMV), graft versus host disease (GVHD), the pretransplant conditioning regimen consisting of total body irradiation and chemotherapeutic agents, and the use of cyclosporin A.

Incidental cases have been described of CMV viremia accompanied by acute renal failure in kidney transplant recipients [28]; histological examination displayed oedema or necrosis of glomerular endothelial cells and platelet thrombi within glomerular capillaries. Yet, no mention was made of microangiopathic haemolysis or thrombocytopenia. Also such cases seem to be exceptional, while CMV infection is frequently present among recipients of renal transplants. TMA following BMT is observed both in patients with and without previous episodes of CMV viraemia. In one study, no differences in the incidence of TMA were noted between groups of patients with different status of CMV infection [16].

Holler et al. [16] have suggested a role for GVHD in the pathogenesis of BMT-associated TMA. They noted an increased incidence in patients who had experienced more severe grades of GVHD, and suggested that GVHD could be related to TMA via cytokine-mediated endothelial damage or via an altered metabolism of cyclosporin A in cases of hepatic GVHD. However, this remains speculative. Also TMA is frequently observed in the absence of GVHD and in autologous transplantsations.

With respect to the conditioning regimen preceding BMT: in nearly all cases this consisted, apart from total body irradiation, of administration of high doses of cyclophosphamide (about 50 mg/kg), sometimes with the addition of cytotoxic agents, or other chemotherapeutic agents. Many cases of severe TMA have been described following the administration of mitomycin-C; only few reports exist of TMA associated with the use of other cytostatic agents. To our knowledge, no reports have been made of cyclophosphamide-induced TMA. Studies in rats have demon-
The other component of the conditioning regimen, total body irradiation (TBI), appears to be the most important, though not exclusive, pathogenetic factor. BMT-associated TMA displays a striking similarity to 'radiation nephritis', both in its clinical presentation and histological features. Radiation nephritis [30,31] can be observed after more than 50% of the kidney volume has been exposed to doses of 20–30 Gy. In BMT, doses of conditioning TBI generally amount to 7.5–14 Gy, administered in one or two fractions; in this setting, dose intensity is comparable to administration of 20–30 Gy in smaller fractions of 1–3 Gy. Following irradiation of the kidneys, TMA with loss of renal function is observed after an interval of about 6–12 months, while BMT-associated TMA is observed after 3–12 months. The delay between irradiation and the onset of microangiopathy could be explained by the fact that radiation primarily induces damage to the mitotic apparatus; the slow rate of replication of endothelial cells (every 2–3 months) would account for clinically important endothelial damage occurring only after several months. Further proof for the causative role of TBI in BMT-associated TMA is obtained both from animal studies and clinical data. TMA was observed in mice when autologous BMT was preceded by TBI only and no chemotherapeutic agents or other drugs were administered [32]. In another study in rats, mortality due to renal failure after autologous BMT was related to the dose of irradiation; renal function remained stable in animals receiving upper-half-body irradiation only [33]. Similar findings were observed in humans by Lawton et al. [24]. They studied 143 patients who were selected for allogeneic BMT. In half of their patients, transmission of radiation to the kidneys was partially blocked, thus reducing the dose of renal irradiation from 14 to 12 Gy. In this group of patients the incidence of BMT-associated TMA was significantly lower than in the control group, i.e. 6% versus 26%. This study underscores the importance of radiation injury in the pathogenesis of BMT nephropathy and also indicates possible ways of reducing its incidence.

Finally, the possible role of cyclosporin A deserves attention. In allogeneic BMT, CsA is often used in order to prevent GvHD [34]. Experience from clinical transplantation shows that CsA can induce changes in renal arterioles, both functional, i.e. vasoconstriction [35], as well as structural, i.e. arteriolopathy resulting in narrowing of the vascular lumen [36]. In vitro, CsA has been shown to induce a dose-related inhibition of prostacyclin production by endothelial cells [37], as well as increased release of thromboxane from platelets and enhanced platelet aggregation [38]. Fibrin thrombi in glomerular capillaries and renal arterioles have been observed in rabbits [39] and humans [36,40] treated with CsA. Also recurrence of HUS in renal allograft recipients [41] and de novo occurrence of HUS after kidney [42] and liver [43] transplantation have been associated with the use of CsA. TMA following BMT has been observed both in patients using CsA and in patients not using this drug (such as our patient receiving an HLA-identical graft). Yet some data indicate that CsA may have a contributory role in causing BMT-associated TMA. Thus, Holler et al. [16] prospectively studied patients following allogeneic BMT: 49 of 66 patients using CsA developed TMA, 10 of whom displayed severe clinical symptoms, while in none of 11 patients receiving methotrexate as GvHD prophylaxis signs of TMA were found. In a study by Silva et al. [20], seven of 112 patients using CsA developed TMA versus one of 146 patients not using CsA; it has to be noted, however, that these data were collected retrospectively, and in two different groups of patients (receiving allogeneic and autologous BMT respectively). The possible role of CsA is further illustrated by the fact that BMT-associated TMA has been described in the absence of previous TBI in patients receiving CsA: 4 of 20 patients treated for aplastic anaemia developed this complication [10]. In the above studies, CsA dosages and serum levels generally were within acceptable ranges.

Though available data thus strongly suggest that TBI and possibly CsA are the most important pathogenetic factors, it has to be pointed out that cases have been described in the absence of CsA and previous TBI [18,21], underscoring the multifactorial genesis of this syndrome.

**Therapy of BMT-associated TMA**

As regards the optimal therapy for BMT-associated TMA: it is difficult to draw firm conclusions from the presently available data. By analogy to other forms of TMA [44,45], inhibitors of platelet aggregation, anticoagulants, corticosteroids, vincristine, plasma infusion and plasma exchange have all been applied, often simultaneously and in an uncontrolled manner. Beneficial effects from therapy most often seemed to be related to the application of plasma exchange (PE) with replacement of fresh frozen plasma [13,15,17,19]. Yet in many cases also PE was without effect [8,12,16,18,20]. Supportive care should consist of replacement of renal function and aggressive treatment of hypertension, in which ACE inhibitors appear to be the drugs of choice. The latter possibly have a beneficial effect on the evolution of TMA: following the development of BMT-associated TMA in rats, treatment with captopril was shown to be associated with a decrease in the amount of proteinuria and renal failure, as well as an increased duration of survival [46].

**References**

Haemolytic uraemic syndrome following bone marrow transplantation


33. Moulder JE, Fish BL, Abrams RA. Renal toxicity following total-body irradiation and syngeneic bone marrow transplantation. Transplantation 1987; 43: 589–592


