

review

Viral-associated thrombotic microangiopathies

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Thrombotic microangiopathies encompass a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia associated with hyaline thrombi (comprised primarily of platelet aggregates in the microcirculation), and varying degrees of end-organ failure. Many primary (genetic) and secondary etiological predisposing factors have been described—namely pregnancy, autoimmune disorders, cancer, drugs and antineoplastic therapy, bone marrow transplantation/solid organ transplantation, and infections. In the setting of infectious diseases, the association with Shiga or Shiga-like exotoxin of *Escherichia coli* 0157:H7 or *Shigella dysenteriae* type 1-induced typical hemolytic uremic syndrome is well known. Recently however, an increasing body of evidence suggests that viruses may also play an important role as trigger factors in the pathogenesis of thrombotic microangiopathies. This is a comprehensive review focusing on the current understanding of viral associated/induced endothelial stimulation and damage that ultimately leads to the development of this life-threatening multisystemic disorder.

A quantum leap has been achieved in the last few years in the understanding of the etiology and the pathophysiology of the thrombotic microangiopathies (TMA), which includes a spectrum of entities like thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TMA is characterized by the central feature of endothelial cell damage or stimulation due to a myriad of insults, leading to secretion of long strings of the ultra-large von Willebrand factor (vWF) multimers that remain anchored to the cell membrane. These multimeric strings are strongly bonded to the glycoprotein Ib α components of platelet glycoprotein Ib α -IX-V surface receptors, causing adherence of platelets and the subsequent aggregation of additional platelets to each other via activated glycoprotein IIb-IIIa receptors. This produces potentially occlusive platelet thrombi, culminating in intravascular platelet clumping.

TTP and HUS usually are pathologically distinct diseases with thrombi rich in vWF and platelets occurring in TTP while platelet-fibrin rich hyaline thrombi occur in diarrhea-associated HUS, suggesting two distinct pathways that cause microvascular thrombosis. The classic pentad (fever, thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, and neurologic symptoms) is typical of TTP but seen

only in 1/3 of patients. In HUS most patients do not have wide-spread systemic symptoms and hematologic complications, but predominately renal involvement. TTP can be subdivided into three types: congenital or familial, idiopathic, and non-idiopathic. The congenital and idiopathic TTP syndromes are caused primarily by deficiency of ADAMTS13, owing to mutations in the ADAMTS13 gene or autoantibodies that inhibit ADAMTS13 activity. Nonidiopathic secondary TTP is associated with conditions like autoimmune diseases and vasculitis (systemic lupus erythematosus, scleroderma) pregnancy/postpartum; cancer; hematopoietic stem cell transplantation, drugs and other antineoplastic agents (gemcitabine, mitomycin C, calcineurin inhibitors, quinine, cocaine, ticlopidine, clopidogrel) and infections. HUS may be classified as either diarrhea-associated (due to enteric infection with Shiga-toxin-producing organisms) or non-diarrhea/atypical (aHUS). aHUS has recently been shown to be a disease of complement dysregulation, with 50% of cases involving the complement regulatory genes, factor H, membrane cofactor protein (MCP/CD46), factor I and factor B. However, incomplete penetrance of mutations in ADAMTS13 or complement regulatory genes strongly supports that precipitating events or triggers are necessary to cause endothelial damage,

Table 1. Summary of the etiology of thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS).

	Etiology
TTP	
Congenital/Familial	Mutations in ADAMTS13 gene
Idiopathic	Antibodies anti-ADAMTS13
Non-idiopathic	Vasculitis, pregnancy, cancer, drugs, solid organ/stem cell transplantation, infections
HUS	Shiga-toxin-producing organisms (<i>Escherichia coli</i> 0157:H7)
aHUS	
50% cases	Mutations in alternative complement pathway regulatory genes; antibodies anti-complement
Remaining cases	Upper respiratory tract infections, gastroenteritis; medications; systemic diseases; malignancy, pregnancy; Inactivation of VEGF and downstream signalling pathway; mutations in thrombomodulin gene; other mechanisms?

which evolves to thrombotic microangiopathy in many patients. Recently, mutations in the thrombomodulin gene and a newly described mechanism of inactivation of pro-angiogenic vascular endothelial growth factor (VEGF) or its signalling mechanisms like the receptor-1 tyrosine kinase signalling mechanism secondary to some drugs (bevacizumab, sunitinib) could promote the formation of intra-arterial platelet aggregation and is therefore a strong risk factor for the development of TMA (Table 1).¹⁻²³

The main focus of this review is to emphasize and raise clinician awareness of the contribution of many types of viruses to endothelial damage, which ultimately leads to the cascade of events culminating in the manifestations of TMA. Multiple viral agents have the capability to induce stimulation of endothelial cells or activation of alternative pathways either alone or synergistically with other co-factors that result in TMA. An overview of the types of viruses and the proposed pathophysiologic mechanisms are summarized below (Table 2).

RNA viruses

Retroviridae family-related TMA

Retroviruses are enveloped viruses that belong to the viral family *Retroviridae*. A retrovirus is an RNA virus that is replicated in a host cell via the enzyme reverse transcriptase to produce DNA from its RNA genome. The DNA is then incorporated into the host's genome by an integrase enzyme. The virus thereafter replicates

as part of the host cell's DNA. Two viruses from this family have been associated with TMA.

Increasingly recognized is TMA associated with the human immunodeficiency virus (HIV) infection, which is the most extensively studied and reported. HIV is a member of the genus *Lentivirus*, part of the family of *Retroviridae*. Over two hundred cases of HIV related TMA or TMA-like syndrome have been reported so far. A detailed review of HIV-related TMA has been discussed elsewhere so this review will focus only on the most important aspects.²⁴⁻²⁶

Both TTP and HUS are associated with HIV infection. Although in the HIV setting TMA occurs in the later stages of infection, there are reports of TMA as a primary manifestation of acute viral infection.²⁷ TMA is more common in HIV-infected individuals than in the normal population. Lower CD4+ cell counts (<100/uL), higher HIV-1 RNA levels, clinical AIDS, opportunistic infections (e.g., CMV or HHV-8 infection), various drugs commonly used in advanced disease, and immune reconstitution after response to combined antiretroviral therapy (cART) are all considered to be potential HIV-related risk factors.²⁸⁻³² Multiple mechanisms have been proposed for the pathophysiology of HIV-related TMA. Complete deficiency of the vWF-cleaving protease ADAMTS13 has been reported in HIV-associated TTP due to development of IgG and occasionally IgA and IgM autoantibodies. There is a contrary argument also, that in HIV-associated TMA, the metalloproteinase levels are generally not decreased, and that an alternative mechanism is responsible for a different pathophysiology than the idiopathic form of TTP.³³⁻³⁶ Demonstration of the virus p24 antigen in the endothelial cell suggests either a direct cytopathic effect of the virus or functional impairment of the endothelium; in another report, specific viral envelope mutations were found in a region known to influence viral endothelial tropism.^{37,38}

In idiopathic TMA, patients who undergo plasmapheresis with or without prednisone have a decrease in mortality rate from almost 100% to 10%. Patients with HIV-associated TMA, who do not have AIDS, have a similar favorable outcome when treated with plasmapheresis. Recently, some reports have shown the efficacy of monoclonal antibodies to HIV-TMA refractory to plasma exchange.^{39,40} While HIV-associated TMA has a good prognosis, similar to that of idiopathic TMA, AIDS-associated TMA has a very poor prognosis. The etiology of the higher mortality in AIDS-associated TMA as compared to HIV-associated TMA remains unclear, but a higher viral burden and HIV-related sec-

ondary complications like opportunistic infections and cancer are considered to be strong contributors. In the later stages of HIV disease, there is a high risk of death from TMA at 1 year (31%-38%), with a significant morbidity and mortality and very poor survival (45% of AIDS patients die within 2 months of virus detection).

HIV patients with HUS present with more severe immunologic deterioration than patients with TTP. Although initial clinical symptoms are fewer than TTP, diagnosing HUS implicates a very poor prognosis with life expectancy rarely exceeding 1 year. With the advent of the era of combined antiretroviral treatment (cART), a visible decline in the incidence of HIV-TMA to values well below 1% of HIV-infected patients has been observed. A high response rate is reported to plasma infusion and anti-retroviral therapy, reducing the need for plasma exchange in treating this complication. This may be due to the reported lower incidence of opportunistic infections and AIDS related tumors.²⁸⁻³²

A point of caution for the clinician is that diagnosis of TMA in HIV patients is tricky. The presence of microangiopathic hemolytic anemia and thrombocytopenia with no underlying cause is non-specific. Because AIDS-related disorders may cause these abnormalities, the diagnosis of TMA is often uncertain in patients with HIV infection.

The HTLV-1 is a human RNA retrovirus from the genus *Deltaretrovirus* and member of the Retroviridae family that causes T-cell leukemia and T-cell lymphoma in adults and may also be involved in certain demyelinating diseases, including tropical spastic paraparesis. To date, only 5 cases of HTLV-1, which responded to plasma exchange or infusion were described as being the causative agent of TTP in previous healthy persons. This suggests that the mechanism of viral-induced TMA is also through the ADAMTS13 function.^{41,42}

Flaviviridae family-related TMA

The hepatitis C virus (HCV) is a small (50 nm in size), enveloped, single-stranded, positive sense RNA virus. It is the only known member of the *Hepacivirus* genus in the family Flaviviridae. Anticardiolipin antibodies (ACA) have been linked with chronic HCV infection. Renal TMA occurring in HCV positive renal allograft recipients with a positive ACA test has been recently reported.⁴³ ADAMTS13 inhibition was also described as a mechanism of HCV-related TMA.⁴⁴ However, most reports show that HCV anti-viral treatment (interferon and pegylated ribavirin) as well as living donor liver transplantation in patients with end-stage liver disease due to HCV infection by themselves are responsible for the pathogenesis of TMA.⁴⁵⁻⁵²

Table 2. Overview of the suspected mechanism of pathogenesis of viral TMA.

Virus	Type of TMA	Mechanism of pathogenesis
RNA viruses		
Retroviridae family		
HIV	TTP/HUS	- Direct endothelial injury - ADAMTS13 deficiency? - Other mechanisms?
HTLV-1	TTP	- ADAMTS13 inhibitors
Flaviviridae family		
Hepatitis C	TTP	- Anticardiolipin antibodies - ADAMTS13 inhibitors
Dengue	TTP	- Direct endothelial injury - ADAMTS13 inhibitors - Immune complex mediated
Reoviridae family		
Rotavirus	HUS	- Unknown
Caliciviridae family		
Norovirus	HUS	- Unknown
Bunyaviridae family		
Crimean-Congo fever virus	TTP	- Cytokine storm-mediated endothelial injury
Picornaviridae family		
Hepatitis A	HUS	- Unknown
Coxsackie; Echovirus	HUS	- Direct endothelial injury
Orthomyxoviridae family		
Influenza A	TTP/HUS/ aHUS	- ADAMTS13 inhibitors - Complement dysfunction
DNA viruses		
Herpesviridae family		
Varicella-zoster virus	aHUS.	- Direct endothelial injury - Complement dysfunction
CMV	TTP/HUS	- Direct endothelial injury - Cytokine storm-mediated endothelial injury
HHV-6	TTP	- Direct endothelial injury - Cytokine storm endothelial injury
EBV	HUS	- Unknown
HHV-8	TTP	- Direct endothelial injury
Adenoviridae family		
Adenovirus	TTP/HUS	- Modulation of endothelial intracellular factors - NK cytotoxicity
Parvoviridae family		
Parvovirus B19	TTP/HUS	- Direct endothelial injury - Immune-complex mediated
Polyomaviridae family		
BK virus	TTP	- Direct endothelial injury

TTP: thrombotic thrombocytopenic purpura; HUS-hemolytic uremic syndrome; aHUS: atypical HUS; HIV-human immunodeficiency virus; HTLV-1: human lymphotropic lymphoma virus-1; CMV: cytomegalovirus; HHV-6: human herpes virus-6; EBV: Epstein-Barr virus; HHV-8: human herpes virus-8

Dengue virus is a single positive-stranded RNA virus of the family *Flaviviridae*; genus *Flavivirus* and infection by this virus also appears to be a contributing factor for TMA. In a reported case, renal biopsy showed TMA with glomerular and arteriolar microthrombi and electron microscopy revealed the presence of microtubuloreticular structures, suggesting a viral infection. The glomerular changes observed in dengue hemorrhagic fever have only been scarcely described and can include a variety of signs, including IgG, IgM, and/or C3 deposition and thickening of the glomerular basal membrane.⁵³ Acquired IgG ADAMTS13 inhibitor during the acute phase of dengue virus infection was recently demonstrated. An excellent response to plasma exchange and disappearance of the anti-ADAMTS13 inhibitor after remission of TMA and dengue resolution was seen in that report.⁵⁴

Reoviridae family-related TMA

Rotavirus is a genus of double-stranded RNA virus in the family *Reoviridae* and is the most common cause of severe diarrhea among infants and young children. Only one case to date of a possible relationship of this virus and TMA was reported in an elderly patient. The presence of the rotavirus in the fecal matter, the absence of other TMA causative factors and the favorable clinical course after viral disappearance favored a causal role in the pathogenesis of TMA.⁵⁵ However, caution is advised for the risk of false positives in stool samples analysis so other diagnostic techniques must be used to confirm the suspected diagnosis.⁵⁶

Caliciviridae family-related TMA

Norovirus (formerly Norwalk agent) is an RNA virus member of the *Caliciviridae* family that causes approximately 90% of non-bacterial outbreaks of gastroenteritis around the world. Only a single case of HUS complicated with norovirus-associated gastroenteritis has been reported so far.⁵⁷ It is unclear as to whether the patient's norovirus infection was a root cause, a simple coincidence, or a precipitating factor for HUS since the patient had chronic kidney disease and hypertension. Further accumulation of clinical studies including case reports is necessary to confirm whether HUS is a real association in patients with norovirus-associated gastroenteritis.

Bunyaviridae family-related TMA

Crimean-Congo hemorrhagic fever (CCHF) virus is a widespread tick-borne viral disease, a zoonosis of domestic animals and wild animals, that may affect humans. The pathogenic virus, especially common in

East and West Africa, belongs to the genus *Nairovirus* and is a member of the *Bunyaviridae* family of RNA viruses. One report showed the association of this infection in a patient that presented with a fatal fulminant picture of TTP. A positive molecular testing for CCHF virus was reported. Several features of that case suggest a cytokine-mediated mechanism for the pathogenesis of CCHF infection.⁵⁸

Picornaviridae family-related TMA

Hepatitis A virus, from the *Hepatovirus* genus and *Picornaviridae* family was described in a single report as the trigger factor for HUS without other recognizable causative etiologic agents.⁵⁹ No other cases have been described so far since hepatitis A infection is generally a self-limited disease.

Coxsackievirus, Echovirus

Sporadic cases of HUS with coxsackie and echovirus were reported in the literature in children and adolescents. The first was reported in 1965, in which coxsackievirus A was isolated from a patient with typical HUS and without other precipitating causal factors.⁶⁰ Subsequently, in 1971, a case of a child with myocarditis due to coxsackievirus B infection and concomitant development of the clinical picture of HUS was reported.⁶¹ Similar cases were later reported.^{62,63} A review of the records of 21 children with HUS seen between 1967 and 1972 revealed a tendency for cases to occur predominantly during the late summer months. Nineteen of these children were studied serologically for evidence of associated infection with coxsackie B viruses, and evidence was found in 15 (79%) of these patients. Coxsackie B viruses were isolated concomitantly from two of the patients.^{62,63}

Echovirus type 22 is another enterovirus with a strong association with HUS in pediatric patients. Eight among 10 patients with HUS had a recent episode of a proved gastroenteritis due to Echovirus 22 according to one study.⁶⁴ Concurrent infection with two or more enteroviruses was described in a cluster of 10 family cases with recent gastroenteritis followed by HUS. This suggests that the various enteroviruses can act synergistically to promote HUS development.⁶⁵ It is known that coxsackie B viruses can attack vascular endothelium, and if disruption of the endothelium occurs, it is possible that vessel-wall collagen could activate platelets and result in intravascular coagulation. The demonstration of coxsackie B4 antigen in the renal tissue supports a direct viral effect.^{65,66}

The possible TMA etiological role of the enterovirus (coxsackie virus and echovirus) was questioned in

a study where investigators stated that verocytotoxin-producing *Escherichia coli* (VTEC) infection causes most cases of HUS. Ten to 30% of patients, however, are negative for VTEC infection. The etiology of HUS in VTEC-negative cases remains poorly understood. The frequency of enteroviral infections was not statistically significant in the acute phase of VTEC-positive and VTEC-negative HUS. Therefore, enteroviral infections should not be considered a cause of HUS in VTEC-negative children.⁶⁷ Although this may be arguable, a patient with HUS and gastroenteritis secondary to enteroviruses strongly supports the viral role in the triggering of the cascade that culminates in TMA.

Orthomyxoviridae family-related TMA

Influenza A virus is an RNA virus, the sole member of the genus *Influenzavirus A*, which belongs to the broader family of Orthomyxoviridae. TMA secondary or induced by influenza A virus infection has been reported several times during the recent pandemic of H1N1 influenza A infection. The proposed pathophysiology of TMA includes in one case the production of anti-ADAMTS13 inhibitors of the IgG type, which produced a clinical picture of TTP that was fatal even after steroid administration and plasma exchange.⁶⁸ Interestingly, there are also three reports showing that inactivated human influenza vaccine may induce TTP bouts by boosting the production of anti-ADAMTS13 autoantibodies.⁶⁹⁻⁷¹

H1N1 and also H1N1-associated bacterial infections have to be considered in HUS and aHUS patients: In a report, aHUS in a patient with a mutation in the gene (CD46) encoding the transmembrane complement regulator membrane cofactor protein was triggered by H1N1 infection and had a good outcome with oseltamivir, plasma exchange and hemodialysis. Two other cases of aHUS were apparently triggered by this virus.⁷²⁻⁷⁴ Although H1N1 influenza A virus may have been the trigger of aHUS in the cases reported here, it remains an interesting but unanswered question whether an underlying complement defect served as a susceptibility factor, at least in a subgroup of patients.⁷⁵ Co-infection with influenza A virus and the bacteria *Streptococcus pneumoniae* may act synergistically to induce HUS via neuraminidase activity since both agents alone were shown to be associated with this clinical picture. The neuraminidase of influenza may even cause erythrocyte fusion and hemolysis.⁷⁶⁻⁷⁸ Another case was described as a late complication of a renal allograft patient with clinical and laboratorial manifestations of HUS. Although immunosuppressive drugs were ruled out as the direct causative agent of HUS since the man-

ifestations occurred concomitantly with an influenza virus infection, the exact mechanism of lesions was not characterized.^{79,80}

DNA viruses

The Herpesviridae are a large family of DNA viruses composed of relatively large double-stranded, linear DNA genomes encoding 100-200 genes encased within an icosahedral protein cage called the capsid, which is itself wrapped in a protein layer called the tegument containing both viral proteins and viral mRNAs and a lipid bilayer membrane called the envelope. This family of DNA viruses are divided into subfamilies:

Alpha-herpes virus subfamily

Only one case of typical HUS complicating varicella-zoster virus (VZV) (*Human herpesvirus 3*) infection was reported so far with autopsy showing diffuse capillary wall thickening and extensive wrinkling of the glomeruli basement membrane with subendothelial deposition of granular material.⁸¹ A second report of two cases of aHUS after VZV infection, with complement dysfunction, one of them having a membrane cofactor protein mutation, and the other anti-factor H antibodies shows that infectious agents such as VZV may be the trigger of aHUS in patients with complement dysregulation and should lead to extensive screening of the complement system in order to identify susceptibility factors.⁸²

Beta-herpes virus subfamily

Cytomegalovirus (CMV) (*Human herpesvirus 5*) infection or reactivation can initiate endothelial inflammation and vasculitis and play a causative role in TMA, resulting in both TTP or HUS clinical manifestations. CMV can directly damage the endothelial cells and can cause platelet adhesion to the microvascular wall by inducing the expression of endothelial adhesion molecules and the release of vWF. In fact, vascular endothelial CMV infection can be detected in about 50% of patients who develop TMA secondary to HIV infection and CMV is very frequently found in patients with AIDS at autopsy since CMV inclusions were detected in kidney specimens obtained from HIV-infected patients with TMA suggesting that co-infection with both virus may promote TMA genesis.⁸³⁻⁸⁹ CMV infection and TMA in the transplant setting (bone marrow/solid organ transplantation) may also occur. One case of CMV-associated TMA after liver transplantation was reported and resolved after anti-viral therapy. In renal allograft recipients, CMV can cause distinctive glomerulopathy

characterized by endothelial damage and mononuclear cell infiltration of glomerular capillaries. Infection with CMV as a trigger for posttransplant TMA in renal allografts has been reported in 8 cases. All patients developed TMA between 4 weeks and 25 years after transplantation. Although in all these cases, the coexistence of multiple factors (transplant, graft-versus-host disease, immunosuppressive drugs) may have contributed to the clinical picture of TMA, the course of disease with onset of TMA within days after onset of CMV disease and the disappearance of hemolysis after negativation of CMV-DNAemia is highly suggestive of a causative role of CMV in the development of posttransplant TMA. Moreover in one case it is highly unlikely that the TMA would have been induced by the immunosuppression since renal transplantation was done 25 years ago and all evidence indicates a CMV-induced TMA. Resolution of TMA after CMV treatment in all these cases, reinforces the notion that CMV infection is an important contributing factor for TMA development.⁹⁰⁻⁹⁶

Human herpesvirus 6 (HHV-6), which is closely related to CMV, is known to infect lymphocytes, monocytes/macrophages, and vascular endothelial cells. It has also been suggested as a potential cause of TMA, leading to activation and damage of endothelial cells more severely than CMV and increased thrombomodulin, and plasminogen activator inhibitor-1 levels. Co-infection with both viruses amplifies endothelial injury. Elevation of cytokine levels both in CMV and HHV-6 infection has been associated with endothelial damage and TMA. HHV-6 infection usually reactivates during immunosuppression due to high-dose chemotherapy in conditioning regimens of bone marrow transplantation. HHV-6-related TMA is an underdiagnosed entity. However, given its rapid lethal course if left untreated and owing to its good response to antiviral therapy the clinician must stay alert for this association and act promptly on minimal clinical and laboratory suspicion.⁹⁷⁻¹⁰⁰

Gama herpes virus subfamily

HUS associated Epstein-Barr virus/*Human herpesvirus 4 (EBV/HHV-4)* was first reported in 1974. Since then, only two more cases have been reported. In the first case EBV developed into thrombocytopenia with HUS during the convalescent phase as an unusual manifestation.¹⁰¹ In the second reported case, in a patient with HUS developing in the context of a infectious mononucleosis with positive IgM-EBV VCA antibody and Epstein-Barr nuclear antigen, supportive care including hemodialysis, plasmapheresis, antihypertensive

medication and aspirin, resolved the clinical picture.¹⁰² In the third case the clinical course was uneventful with mild HUS manifestations.¹⁰³ The rarity of EBV-related TMA probably stems from the absence of CD21 antigen on the glomerular endothelial cells which is the cellular receptor for EBV, implying that other mechanisms besides a direct cytopathic effect is responsible for the endothelial damage that leads to TMA.¹⁰⁴

Human herpesvirus 8 (HHV-8) infection (Kaposi sarcoma-associated herpesvirus), which is common among advanced stage disease HIV-infected patients, involves vascular endothelial cells and may contribute to the development of TMA by direct endothelial injury or stimulation and thus potentiating the effects of HIV-related TMA.¹⁰⁵

Adenoviridae family-related TMA

Adenoviruses are medium-sized (90–100 nm), nonenveloped icosahedral viruses composed of a nucleocapsid and a double-stranded linear DNA genome and are members of the Adenoviridae family. There are 55 described serotypes in humans, which are responsible for 5% to 10% of upper respiratory infections in children, and many infections in adults as well. Adenoviruses are increasingly recognized as a significant cause of morbidity and mortality in immunocompromised patients. Disseminated adenoviral disease has been associated with fatal cases of TTP and HUS, one after allogeneic bone marrow transplantation and another in an AIDS patient with disseminated adenovirus and cytomegalovirus co-infection, respectively. The proposed mechanism of adenovirus induced endothelial damage may be modulation of expression of endothelial intracellular factors that increase natural killer cell-mediated cytotoxicity.^{88,106,107}

Parvoviridae family-related TMA

Parvovirus B19 (*Human parvovirus B19*), an erythrovirus member of the Parvoviridae family of small DNA viruses, is a non-enveloped, icosahedral virus that contains a single-stranded linear DNA genome and is the etiologic agent of aplastic anemia. TTP and HUS were associated with parvovirus B19 infection both in immunocompetent and immunosuppressed individuals. Super-infection of this virus in a HUS patient with *E coli* 0157:H7 may amplify the clinical and laboratory manifestations. TMA-related parvovirus B19 infection developing after renal transplantation was demonstrated by a typical clinical picture allied by a positive polymerase chain reaction amplification of viral DNA in the renal biopsy specimens along with positive IgM serology and profound reticulocytopenia. Parvovirus B19-related TMA may also precede allograft vasculitis

in renal transplant recipients. The temporal association between aplastic anemia and the onset of thrombotic graft microangiopathy, isolation of the viral genome in renal specimens, seroconversion, endothelial tropism of the virus (the receptor for parvovirus B19 on erythrocytes, the P antigen, is also present on endothelial cells) and possibly production of circulating immune complexes suggest that parvovirus B19 could be the etiologic agent of TMA in these cases. A high index of suspicion is required for early diagnosis and treatment of parvovirus B-19 infection.¹⁰⁸⁻¹¹⁴

Polyomaviridae family-related TMA

BK virus (BKV), a double-stranded DNA virus, is a member of the Polyomaviridae family. BKV-related TMA was recently described for the first time in an allogeneic hematopoietic stem cell transplant patient, in whom the disease developed many years after the procedure as a proved BKV encephalitis that was complicated by a fulminant clinical picture of TTP. Although many factors may have triggered the TMA (graft-versus-host disease, calcineurin inhibitors), ultimately BKV infection appeared to be the precipitating factor in a susceptible host in this case. BKV has also been associated with a fatal case of vasculopathy in a renal allograft patient, in which disseminated endothelial infection by BKV was proved.¹¹⁶ BKV may

have a direct cytopathic effect in endothelial injury, but other mechanisms may be responsible for the pathogenesis of TMA in this type of infection. More cases are needed to confirm this and the clinician must be aware of this association.

Conclusions

Viruses are important etiologic agents in the pathogenesis of TMA.^{117,118} Some have a propensity to induce TTP while others are only associated with HUS or aHUS. The exact pathophysiology of viral-associated TMA remains to be elucidated. However, direct endothelial cell injury appears to play an important role. Host genetic or ambient susceptibility factors may create a favorable ground for the viruses to trigger the cascade of events that culminates in the clinical manifestations of TMA. Although some claims of viral-related TMA appear only in anecdotal reports, one cannot reject the possibility of such associations. More cases must be reported to consolidate and reinforce the causal relationship in such circumstances. Clinician awareness is vital when TMA occurs in the context of a viral infection in the absence or even in the presence of confounding initiating factors, since prompt recognition of the clinical picture may be life-saving.

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