Thrombosis associated with acute cytomegalovirus infection: a narrative review

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Abstract

Thrombosis associated with acute cytomegalovirus infection has been reported many times in the literature since the mid 1980s – mainly in case reports and in small case series, but also in four controlled studies. Still, many physicians are unaware of this association although acute cytomegalovirus infection diagnosis in a thrombosis patient may warrant antiviral therapy and may affect anticoagulation therapy duration. Accordingly, the clinical characteristics of patients with thrombosis and acute cytomegalovirus infection are reviewed, and the current knowledge concerning this unique association is presented herein. We believe it is time to add acute cytomegalovirus infection to the list of thrombosis triggers.

Key words: anti-phospholipid antibodies, cytomegalovirus, thrombosis.

Introduction

Thrombosis associated with acute cytomegalovirus (CMV) infection has been reported many times in the literature since 1984 [1] – mainly in case reports and in small case series. In 2011 we reviewed 97 case reports and one case-control study concerning this association [2]. Since then, 16 more case reports and three more controlled studies concerning thrombosis associated with acute CMV infection have been published [3–22]. Still, many physicians are unaware of this association although acute CMV infection diagnosis in a thrombosis patient may warrant antiviral therapy and may affect anticoagulation therapy duration. Accordingly, the clinical characteristics of patients with thrombosis and acute CMV infection are reviewed and the current updated knowledge concerning this unique association is presented herein. We seek to increase awareness of symptoms and signs of acute CMV infection in thrombosis patients as well as symptoms and signs of thrombosis in acute CMV infection patients.

Methods

A literature search was conducted in PubMed and in Google for all-language reports concerning thrombosis associated with acute CMV infection published until July, 2013. Apart from "cytomegalovirus", the search keywords included: "Budd-Chiari", "emboli", "embolism", "infarct", "infarc-

tion", "ischemia", "thrombi", "thromboembolism", "thromboses", "thrombosis", "thrombus", and "thrombotic". Detailed reports presented in scientific meetings and published in peer-review journals and in proceedings were included as well [15]. References from each report were further reviewed for additional reports. Overall, 78 reports concerning 113 patients were reviewed [1–18].

Epidemiology

Mean age of reported patients is 41.7 ±14.6 years (range: 17–83 years) [1–18]. Overall, the female-male ratio is 1 : 1 in all reported patients. However, the female-male ratio is 1.6 : 1 in controlled studies that included consecutive patients with thrombosis and acute CMV infection [19–21].

The incidence of thrombosis among hospitalized patients with acute CMV infection has been studied once by Atzmony *et al.* [21]; they retrospectively studied the incidence of venous as well as arterial thromboses among 140 consecutive patients with acute CMV infection and among 140 matched controls admitted to a tertiary medical center; according to their results, the incidence of thrombosis among hospitalized patients with acute CMV infection is 6.4%: 5 (3.6%) patients had arterial thrombosis and 4 (2.9%) patients had venous thrombosis. The true incidence of thrombosis among hospitalized patients with acute CMV infection is probably higher, since not all patients in their study had undergone imaging studies aimed at excluding thrombosis.

The incidence of thrombosis among out-patients following acute CMV infection has been studied once by Paran *et al.* [22]; they retrospectively studied the incidence of venous thrombosis among 6205 patients 6 months following acute CMV infection and among 84 310 controls without CMV infection in a large health maintenance organization; according to their results, the incidence of venous thrombosis per 1000 capita is 3.06, i.e., 19 (0.3%) patients had thrombosis. The true incidence of thrombosis among out-patients following acute CMV infection is also probably higher, once again, since not all patients in their study had undergone imaging studies aimed at excluding thrombosis.

The incidence of acute CMV infection among hospitalized thrombosis patients has been studied twice: Tichelaar *et al.* [19] prospectively studied the incidence of acute CMV infection among 258 hospitalized venous thrombosis patients and among 139 controls, and found that it was 1.9% (n = 5); Schimanski *et al.* [20] prospectively studied the incidence of acute CMV infection among 166 hospitalized venous thrombosis patients and among 166 healthy blood donors, and found that it ranged between 4.3% and 7.4% in the general population of venous thrombosis patients and in unprovoked venous thrombosis patients, respectively.

An independent association between thrombosis and acute CMV infection has been demonstrated three times in the literature: in a general population of out-patients [22], in a general population of hospitalized patients [21], and in renal transplant recipients [23].

Pathophysiology

Several theories suggest that CMV infects endothelial cells and enhances the expression of adhesion molecules and tissue factors on their surfaces, thus triggering platelet adhesion and aggregation on vessel walls [24, 25], factor X activation, and thrombin formation [26, 27]. Another theory suggests that CMV increases circulatory levels of Von-Willebrand factor and factor VIII [28, 29]. According to Schimanski *et al.* [20], who prospectively studied the incidence of acute CMV infection as well as factor VIII plasma levels among 166 hospitalized venous thrombosis patients, 3 out of 7 (42.9%) patients with venous thrombosis and acute CMV infection also had high factor VIII plasma levels.

The most accepted theory indicates that acute CMV infection is associated with transient appearance of anti-phospholipid antibodies. This theory has been demonstrated *in vitro* [30] as well as *in vivo* several times [10, 11, 15, 31–37]. According to Schimanski *et al.* [20], who prospectively studied the incidence of acute CMV infection as well as anti-phospholipid antibody seropositivity among 166 hospitalized venous thrombosis patients, 1 out of 7 (14.3%) patients with venous thrombosis and acute CMV infection was also positive for anti-phospholipid antibodies.

Immunological status

The first reported patients with thrombosis and acute CMV infection in the mid 1980s and in the early 1990s were mainly immunocompromised – HIV patients and transplant recipients. Since the mid 1990s, most reported patients have been immunocompetent [1–18]. Acute CMV infection has been considered a benign infection in immunocompetent patients for many years; hence, these trends in reporting possibly reflect the increasing awareness of physicians about thrombosis associated with acute CMV infection in immunocompetent patients as well [38].

Two controlled studies have addressed the immunological status of thrombosis patients with acute CMV infection: according to Atzmony *et al.* [21], out of 9 patients, 6 (66.7%) were immunocompromised and 3 (33.4%) were immunocompetent; according to Tichelaar *et al.* [19], all 5 (100.0%) patients were immunocompetent.

According to published reports, most patients with thrombosis and acute CMV infection are immunocompetent (n = 79; 69.9%). Among 34 immunocompromised patients, 14 (41.2%) patients were solid organ recipients, 8 (23.5%) patients had HIV infection, 6 (17.6%) patients had been taking steroids and/or immunosuppressant agents on a regular basis, 4 (11.8%) patients had active malignancy, 1 (2.9%) patient had undergone splenectomy, and 1 (2.9%) patient has had severe burns [1–18].

Cytomegalovirus infection characteristics

The CMV mononucleosis and/or hepatitis are the two most prevalent CMV diseases in thrombosis patients (n = 76; 67.3%), followed by CMV colitis (n = 10; 8.8%). Other CMV diseases in thrombosis patients include: retinitis (n = 5; 4.4%), pneumonitis (n = 1; 0.9%), encephalitis (n = 1; 0.9%), and Guillain-Barré syndrome (n = 1; 0.9%). Six (5.3%) patients had acute CMV infection without clinical manifestations of CMV disease, e.g., diagnosed by means of serology tests and/or by markers of viremia tested in the course of investigating fever of unknown origin. Other reports are incomplete [1–18].

Although some believe that secondary CMV infection or reactivation of CMV is more thrombogenic than primary CMV infection [20], according to published reports, it is impossible to determine most (n = 94; 83.2%) of the times whether acute CMV infection is primary or secondary since previous serology tests are missing or current serology tests during active infection are incomplete [1–18]. The CMV IgG avidity test is also seldom used [9, 14, 39, 40].

Thrombosis sites

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two most prevalent thromboses associated with acute CMV infection (n = 63; 55.8%), followed by splanchnic vein thrombosis (n = 31; 27.4%) [1–18]. While DVT and PE are more prevalent among immunocompromised patients, splanchnic vein thrombosis is more prevalent among immunocompetent patients [2].

Venous thromboses are associated with acute CMV infection. However, the association between arterial thromboses and acute CMV infection is questionable [22]. Indeed, arterial thromboses associated with acute CMV infection have been seldom reported in the literature [2] and include: renal infarct and renal artery thrombosis (n = 2; 1.8%), stroke (n = 2; 1.8%), myocardial infarction (n = 1; 0.9%), and digital ischemia (n = 1; 0.9%) [7, 11, 21, 32, 41, 42]. Splenic infarct, reported 13 (11.5%) times in the literature [1–18], may be attributed to arterial insufficiency associated with rapid splenic growth, but it may also be associated with arterial embolism [43, 44].

Triggers and predispositions for thrombosis

Apart from acute CMV infection, most (n = 68; 60.2%) patients have other transient triggers and/or chronic predispositions for thrombosis. Use of contraceptives/hormones (n = 17; 15.0%) and factor V Leiden mutation (n = 12; 10.6%) are the two most common triggers and predispositions for thrombosis [1–18]. This phenomenon is true for immunocompetent patients [45] as well as for immunocompromised patients, although triggers and predispositions for thrombosis are more common among immunocompetent patients [2].

Atzmony *et al.* [21] used a regression analysis to study independent triggers and predispositions for thrombosis in acute CMV infection patients; they found that use of contraceptives/hormones and pregnancy are associated with thrombosis. These findings are consistent with those of Tichelaar *et al.* [19]: 3 out of 5 (60.0%) thrombosis patients with acute CMV infection had been taking contraceptives/hormones and 1 (20.0%) patient was postpartum. Also consistent with these findings are those of Schimanski *et al.* [20]: 2 out of 7 (28.6%) thrombosis patients with acute CMV infection had been taking contraceptives/hormones and one (14.3%) patient was pregnant.

Anticoagulation and antiviral therapy

Anticoagulation therapy duration has ranged between a few weeks and one year, but it is not mentioned in most (n = 72; 63.7%) reports [1–18]. In a few reports anticoagulation therapy has been stopped following the disappearance of anti-phospholipid antibodies [32, 36] or following the resolution of thrombosis in imaging studies [17, 18].

Overall, 34 (30.1%) patients have been treated with antiviral agents, i.e., ganciclovir and/or valganciclovir, and most of them (n = 25; 73.5%) have had viremia diagnosed by mean of DNA PCR and/or antigenemia assays [1–18]. Immunocompromised patients have been treated with antiviral agents more frequently than immunocompetent patients [2].

Mortality

Overall, 5 (4.4%) patients have been reported dead; all of these patients have been immunocompromised [21, 42, 46, 47]. Mortality is probably higher since case reports may be biased towards a better outcome. Indeed, according to Atzmony *et al.* [21], in-hospital mortality rates among patients with thrombosis and acute CMV infection are 22.2%. To the best of our knowledge, long-term mortality and out-of-hospital mortality

have never been studied in patients with thrombosis and acute CMV infection.

Clinical implications

It is too early and probably not cost-effective to look for thrombosis in every acute CMV infection patient or to look for acute CMV infection in every thrombosis patient. However, since acute CMV infection may be asymptomatic [38], and since serology tests are neither expensive nor harmful, we do believe that acute CMV infection should be looked for by means of serology tests in patients with idiopathic thrombosis, i.e., patients in whom no other obvious risk factors for thrombosis have been identified.

Since acute CMV infection is associated with transient appearance of anti-phospholipid antibodies [10, 11, 15, 20, 30–37], we believe that CMV serology tests should be carried out in thrombosis patients with anti-phospholipid antibodies. Anti-phospholipid antibody serology tests should also be repeated a few months later in order to determine whether seropositivity is transient or permanent. Accordingly, anticoagulation therapy may be stopped following the disappearance of anti-phospholipid antibodies [32, 36].

Research implications

There is a true need to prospectively study the long-term and out-of-hospital morbidity and mortality associated with thrombosis in acute CMV infection patients relative to other thrombosis patients. A clinical study focusing on the incidence of anti-phospholipid antibodies' appearance in acute CMV infection patients is also warranted. It has been recently studied in acute Epstein-Barr infection patients [48], and the results are probably comparable.

Thrombosis triggered by acute CMV infection should be studied in thrombosis animal models in comparison to other infectious organisms. Higher incidence in female patients and the association with use of contraceptives/hormones and pregnancy [19, 20, 22] also raise the question of gender differences and hormonal factors. Gender differences in patients with thrombosis and acute CMV infection may be addressed by basic research in thrombosis animal models as well.

Summary

Thrombosis associated with acute CMV infection is not rare, and it might be related to considerable in-hospital mortality. Acute CMV infection diagnosis in a thrombosis patient may warrant antiviral therapy and may affect anticoagulation therapy duration. Hence, we believe it is time to add acute CMV infection to the list of thrombosis triggers. Physicians should be alert to symptoms and signs of acute CMV infection in thrombosis patients and to symptoms and signs of thrombosis in acute CMV infection patients.

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