Cytomegalovirus infection in a patient with systemic lupus erythematosus and acute myocardial infarction – cause or causal relationship?

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ABSTRACT
The possible role of infectious and inflammatory states in the pathogenesis of atherosclerotic disease has been a matter of debate in the literature. There are case reports of active cytomegalovirus (CMV) infection unmasking underlying dormant systemic lupus erythematosus (SLE). CMV infection has also been postulated to be associated with atherosclerosis development in the coronaries. We present a unique case where a patient with newly diagnosed SLE and acute myocardial infarction was found to have high anti-CMV titers suggesting concomitant active CMV infection. A literature review has postulated strong affiliation of CMV infection with the development of coronary artery disease, an avenue which has yet to be explored further by ongoing research.

1. Introduction
The possible role of infectious and inflammatory states in the pathogenesis of atherosclerotic disease has been a matter of debate in the literature. There are case reports of active cytomegalovirus (CMV) infection unmasking underlying dormant systemic lupus erythematosus (SLE). CMV infection has also been postulated to be associated with atherosclerosis development in the coronaries. We present a unique case where a patient with newly diagnosed SLE and acute myocardial infarction (AMI) was found to have high anti-CMV titers suggesting concomitant active CMV infection.

2. Case presentation
A 60-year-old female presented with a 3-week history of tongue swelling, periorbital edema, and conjunctival injection. Associated symptoms included generalized fatigue, diffuse arthralgias, and a rash. Medical history was significant for well controlled hypertension. Physical examination was significant for tongue edema, right mandibular lymph node enlargement, a petechial rash on legs and buccal mucosa (Figures 1 and 2) and ridged nails (Figure 3). Significant laboratory investigations included: WBC 4.8 K/ul (4.0–11.0), Hb 10.7 gm/dl (12.0–15.0), Hct 33.5% (39.0–43.0), platelets 302 K/ul (125–490), AST 85U/L (<33), ALT 75U/L (<32), ESR 98 mm/h (0–20), CRP 9.0 mg/L (0–5), positive ANA, RF 86 IU/mL (1–3), C3 26 mg/dL (90–180), C4 2 mg/dL (10–40), total complement (CH50) 0 CAE units (60–144). A computed tomography scan of the neck showed multiple bilateral lymph nodes throughout the neck. At this point, her presentation was highly suspicious for an autoimmune process. Additional investigations were ordered; she was empirically started on steroids and discharged with outpatient rheumatology follow-up. The following day she returned complaining of severe epigastric pain and nausea. Electrocardiogram was significant for ST segment elevation in leads II, III, and aVF (Figure 4) and troponin 2.04 ng/mL. She was diagnosed as having acute ST segment elevation myocardial infarction. Cardiac catheterization revealed 90% stenosis of the left circumflex, a drug-eluting stent was inserted. Lipids and HbA1c were ordered to further risk stratify her; results were total cholesterol 168 mg/dl (<200), LDL 96 mg/dl (<100), HDL 34 mg/dl (>50), and HbA1C 5.3% (3.6–5.6). By this time the results for the tests that had been ordered during her previous admission were available; the most salient ones were negative anti-CCP, anti-Ds DNA 1:640 (<1:10), SS-A/Ro 52KDa Ab 182(0–40), SS-A/Ro 60 KDa Ab 112 (0–40), SSB/La IgG Ab 107 (0–40), negative serologies for HIV, hepatitis A/B/C, parvovirus and syphilis. Surprisingly CMV IgG Ab was >10.0 U/mL (N < 0.59 U/mL) and CMV IgM Ab was markedly elevated at 233.0 AU/mL (N < 29.9 AU/mL) consistent with SLE and acute CMV infection. Given these findings, we hypothesized acute CMV infection triggered or at least contributed to her myocardial infarction.

3. Discussion
Cytomegalovirus has been reported to be associated with atheromatous disease. In one study, anti-CMV
IgG was positive in 70% of patients with coronary artery disease (CAD) as compared to 54% in those without. The prevalence of CAD was found to be higher in the subgroup with elevated CRP and anti-CMV antibodies (87%), while only 22% of individuals without CAD had both CMV seropositivity and elevated CRP [1]. CMV is proinflammatory in nature; in mice models, CMV infection has been shown to be associated with elevated levels of inflammatory markers and increased incidence of atherosclerotic lesions in the vessel walls [2]. Various epidemiological studies have hypothesized about the inflammatory role of CMV in the pathogenesis of atherosclerosis [3]. Elevated levels of acute phase reactants in the form of CPR have been found to coexist with CMV in various studies. When adjusted for traditional risk

Figure 1. Petechial rash found in the distal third of the legs and the feet.

Figure 2. Petechial rash on buccal mucosa.
factors for CAD, there is a positive correlation between elevated CRP and CMV seropositivity in patients with underlying CAD [4]. Another study found that in men an elevated CRP level was a significant determinant of CAD even after adjustment for traditional CAD risk factors; in contrast, in women CMV seropositivity was independently predictive of CAD [5]. This suggested there might be variability in the type of immune response a particular host has, which may be responsible for the atherogenic effect of CMV [6]. Acute inflammation over an area of unstable plaque has been well established as cause of AMI, but the trigger for this inflammation is unclear. Various studies looking into possible infectious etiologies have shown active CMV replication in patients presenting with AMI [7,8].

CMV is also an immunomodulatory virus; it has been reported to be associated with SLE by causing de novo disease or exacerbating a known disease. The mechanism by which this occurs is unclear, but it is hypothesized to induce antibodies to U1 snRNP. CMV antibodies cross-react with Sn/RNP autoantigens in SLE patients and can induce anti-La autoantibodies accounting for flares in CMV-infected patients [9]. SLE has been established as contributing to accelerated atherosclerosis via ongoing inflammation. The cardiac risk associated with SLE and/or CMV infection cannot be quantified based on any of the traditional risk scores (e.g. Framingham, ASCVD) [10].

Although an association between CMV infection and atherosclerosis has been postulated in the past, there are no studies available that have established a causal
relationship. This case report adds to the literature highlighting the need for further studies to evaluate if early detection and treatment of CMV in this cohort will lead to improve outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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