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BRIEF REPORT

IgM Positivity for Both EBV and CMV: A Clinical Conundrum

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A review of 28 patients who tested positive for both Epstein-Barr virus and cytomegalovirus immunoglobulin M at an academic medical center revealed that dual positivity is more common than previously reported. These cases require careful review of the history and sometimes supplemental testing. This report highlights features of patients with dual positivity and provides recommendations on interpretation of the results.

Keywords. EBV and CMV IgM; dual positivity.

Infectious mononucleosis (IM) is a clinical syndrome of the reticuloendothelial and lymphatic system, mostly caused by Epstein-Barr virus (EBV) but also by other infections, including cytomegalovirus (CMV) [1]. Given the significant overlap of symptoms between acute EBV and CMV, it is difficult to distinguish EBV- from CMV-related mononucleosis. Exudative pharyngitis, cervical lymphadenopathy, and splenomegaly are more commonly associated with EBV mononucleosis, whereas individuals with CMV mononucleosis tend to have prolonged fevers and systemic symptoms. While in most cases both EBV- and CMV-induced mononucleosis resolve without specific therapy, in certain hosts, determining the specific cause of mononucleosis is important. For instance, primary CMV mononucleosis in pregnant women can cause maternal–fetal CMV transmission. Antiviral therapy such as ganciclovir, valganciclovir, or foscarnet may be indicated in immunocompromised individuals with CMV end-organ disease and/or high viral loads as well as in immunocompetent patients with protracted CMV mononucleosis with severe organ-specific complications of CMV.

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EBV and CMV, members of the herpesvirus family, establish lifelong latent infection and can reactivate. More than 90% of adults have acquired at least EBV or CMV. EBV rates vary widely by age, geographic location, and race/ethnicity. A US-based National Health Examination Survey conducted among 9300 individuals aged 6–19 years between 2003 and 2010 showed that overall age-adjusted EBV seropositivity declined from 72% in 2003–2004 to 65% in 2009–2010, and from 88% among Mexican Americans and 88% among non-Hispanic Blacks to 64% among non-Hispanic Whites [2]. CMV follows similar seroprevalence trends. The US-based National Health Examination Survey conducted among >15 000 individuals aged 6–49 years between 1999 and 2004 showed an overall age-adjusted CMV seroprevalence of 50.4% [3]. With high baseline seropositivity rates, it is important to note that many patients undergoing testing for acute EBV and/or CMV infection may already have latent EBV and/or CMV.

A definitive diagnosis of acute EBV or CMV infection can be made by testing for specific immunoglobulin M and G (IgM and IgG) antibodies against EBV or CMV antigens in the right clinical context. Antibodies against EBV are formed to viral capsid antigens (VCAs), nonstructural proteins expressed early in the lytic cycle, and nuclear antigens (EBNA) expressed during latent infections and appear late during infectious mononucleosis. Acute primary EBV infection demonstrates positive EBV VCA IgM and IgG with negative EBNA, while past EBV infection shows positive EBNA and positive EBV VCA IgG with negative EBV VCA IgM. Acute CMV infection demonstrates positive CMV IgM and IgG, while past CMV infection shows negative CMV IgM with positive CMV IgG. EBV and CMV viral loads are not recommended as first-line tests for diagnosing suspected primary EBV or CMV infection, respectively, but may be useful as adjunctive tests to aid in diagnosis when serologic testing in not conclusive. This is particularly important in high-risk patients to assess disease severity and monitor response to therapy. IgM assays generally have a weaker IgM binding affinity to antigen compared with IgG binding affinity secondary to the antibody maturation effect. Further, the peptide used in the EBV IgM assay is small and synthesized, whereas the CMV IgM assay uses a whole-virus extract as the target antigen, which leads to a higher likelihood of contamination with cell proteins, and thereby higher chances of false positivity.

We noted that some people with mononucleosis syndromes may have simultaneous positivity of both EBV VCA IgM and CMV IgM, resulting in a diagnostic dilemma, as dual positivity could represent multiple different possibilities, including (1) acute infection due to EBV with false-positive CMV serology (which itself could be due to heterophile antibodies or viral

reactivation); (2) acute infection due to CMV with false-positive EBV serology (due to viral reactivation); (3) sequential acute infections by EBV/CMV in either order with prolonged IgM positivity from the first infection; (4) simultaneous acute infection by EBV/CMV; (5) IM-like syndrome due to another etiology with false-positive EBV/CMV serology (which could be due to heterophile antibodies or viral reactivation). While there are data surrounding dual positivity of EBV and CMV serologies in pediatric populations in primary care offices [4, 5], there is a paucity of information surrounding interpretation of dual positivity in adults, especially in hospitalized immunocompromised hosts. The aim of this retrospective study was to ascertain the frequency of dual positivity of EBV VCA IgM and CMV IgM among adults tested in an academic medical center in urban Boston, with the goals of describing patients' clinical characteristics and assisting in interpreting these and subsequent diagnostic tests.

METHODS

The Clinical Microbiology Laboratory at the Brigham and Women's Hospital performs EBV and CMV serologic testing for inpatients in an academic tertiary care hospital, and for outpatients in its affiliated clinics. A small number of specimens from pediatric patients are tested from a few community clinics that also utilize the hospital's laboratory services.

Among patients who underwent EBV VCA IgM and CMV IgM testing using the Liaison assay (DiaSorin, Saluggia, Italy) at Brigham and Women's Hospital between January 1, 2016, and January 1, 2021, we investigated those who were positive for both EBV VCA IgM and CMV IgM. Their electronic medical records were reviewed to collect demographic and clinical characteristics and laboratory information, which included EBV VCA IgM, EBV VCA IgG, EBNA IgG, EBV early Ag IgG, EBV viral load, CMV IgM, CMV IgG, and CMV viral load.

The Institutional Review Board at Mass General Brigham approved the study. Two physicians independently investigated medical records. Cases were stratified based on age, gender, comorbidities, and need for hospitalization. On the basis of clinical history, additional laboratory values, relevant imaging, and treating physician's assessment on chart review, the reviewing physician interpreted dual positive serologies into 1 of 5 broad categories—acute EBV, acute CMV, coinfection/dual infection suspected, other nonherpes infection, and equivocal/unclear.

RESULTS

Between 2016 and 2021, the BWH Clinical Microbiology Laboratory performed EBV VCA IgM tests on 4962 patients, of whom 885 had duplicate testing. Of 4077 unique patients, 268 (6.6%) tested positive, 6 were indeterminate, 32 were equivocal, and the rest tested negative; 49.6% were male, and 50.4% were female. Outpatients accounted for 2840 (69.6%) of specimens, inpatients 1143 (28%), and emergency room 102 (2.5%). The average age of patients tested was 47.3 years, and 3886 (95.1%) of the specimens were from patients aged ≥18 years, consistent with the predominantly adult population served by the hospital and its clinics. Ninety-nine percent of the pediatric specimens were from outpatients.

Table 1. Clinical Characteristics of Patients With Positive EBV VCA IgM Results who Also Tested Positive for CMV IgM

Clinical Characteristics	No. (%)
Mean age, y	36.1
Age range, y	
(i) 4–18	3 (11)
(ii) 19–34	11 (39)
(iii) 35–50	11 (39)
(iv) 51–73	3 (11)
Male	15 (54)
Significant comorbidities	16 (57)
Immunocompromised	7 (25)
Hospitalized	14 (50)
Acuity of symptoms	
(i) Acute (<2 wk)	13 (46)
(ii) Subacute (2–6 wk)	11 (39)
(iii) Chronic (>6 wk)	4 (14)
Clinical presentation	
Fever, chills, diaphoresis, and malaise	18 (64)
Atypical lymphocytosis	14 (50)
Transaminitis	9 (32)
Lymphadenopathy	6 (21)
Splenomegaly	5 (18)
Laboratory testing	
Heterophile antibody positive	6/17 (35)
EBV IgG positive	25/27 (93)
EBV early antigen IgG positive	8/9 (89)
EBNA IgG positive	8/15 (53)
EBV PCR detectable	8/18 (44)
CMV IgG positive	13/22 (59)
CMV PCR detectable	8/20 (40)
Follow-up serologies ordered	6 (21)

Assays used: EBV-specific serologies: Liaison assay (DiaSorin, Saluggia, Italy); CMV serologies: Liaison assay (DiaSorin, Saluggia, Italy); EBV PCR: EBV *m*2000 RealTime System (Abbott Molecular Inc., Des Plaines, IL, USA); CMV PCR: COBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Molecular Diagnostics, Branchburg, NJ, USA).

Abbreviations: CMV, cytomegalovirus; EBNA, nuclear antigen; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; VCA, viral capsid antigen.

Of 268 unique EBV IgM–positive cases, 115 cases had CMV IgM testing performed during the same encounter, and in certain exceptions, during the same week. Dual testing for both EBV and CMV was done in individuals presenting with mononucleosis-like syndrome to assist with diagnosis. Of these, 28 were also positive for CMV IgM (dual positivity), or 24.4% of those for whom both EBV VCA IgM and CMV IgM tests were ordered who had positive EBV VCA IgM results.

A summary of clinical and laboratory characteristics of these patients with dual IgM positivity is shown in Table 1. For those who had dual positive serologies, the mean age was 36.1 years: 3

Table 2. Case Summary of Patients With Positive EBV VCA IGM Results who Also Tested Positive for CMV IgM

Pt ID	Age/ Sex	Immunocompromised	Presenting Symptoms and Signs	Heterophile Ab	EBV VCA IgM	EBV VCA IgG	EBV Early Ag, IgG	EBV EBNA, IgG	EBV DNA, IU/mL	CMV IgM	CMV IgG	CMV DNA, IU/mL	Follow-up Serology	Final Interpretation	Management/ Outcomes/Other Coexisting Illness
1	48/M	No	Abdominal and chest pain[a]	Pos	Pos	Pos	…	…	Detected; 752	Pos	Pos	Not detected	No	Acute EBV infection[n]	Also diagnosed and treated for Lyme disease and babesiosis
2	26/F	No	Night sweats, cervical lymphadenopathy	Pos	Pos	Pos	…	Neg	…	Pos	…	…	No	Acute EBV infection[b]	Two weeks later, symptoms resolved except minimal fatigue
3	47/F	Heart transplant recipient	Nasal congestion, cough, diarrhea[a]	…	Pos	Neg	…	Pos	…	Pos	…	Detected; <137	No	Unclear[b]	Cardiogenic shock thought to be precipitated by nonspecific viral infection, patient died
4	73/M	Heart transplant recipient	Volume overload, dyspnea[a]	…	Pos	Pos	…	…	Not detected	Pos	Pos	Not detected	No	Unclear[b]	CHF exacerbation; EBV/ CMV tests done to workup pulmonary nodules in transplant patient
5	43/M	No	Petechiae, fatigue, headaches[a]	…	Pos	…	Pos	…	Not detected	Pos	…	Detected; <137	No	Unclear	ITP thought to be precipitated by a possible viral infection; platelet count improved with steroids
6	46/M	No	Nasal congestion, eye irritation, headache, cough, neck rash	Neg	Pos	Pos	…	Pos	…	Pos	…	…	No	Unclear	Treated for ehrlichiosis 1 mo prior; self-limiting symptoms, improved without follow-up
7	18/M	No	Sore throat, abdominal pain, fatigue, cervical lymphadenopathy	Pos	Pos	Pos	…	…	…	Pos	Neg	…	No	Acute EBV infection	Saw multiple providers over 3- wk period with persistent symptoms that eventually improved
8	60/F	GCA on steroids	Worsening from baseline GCA headache	…	Pos	Pos	…	…	…	Pos	Pos	…	No	Unclear	Viral studies sent by patient's rheumatologist for persistent acute on chronic headaches
9	47/F	No	Myalgias, headaches, fatigue, poor appetite, diarrhea, cervical lymphadenopathy	…	Pos	Pos	Pos	Neg	…	Pos	Neg	…	No	Dual infection	Recently treated for Lyme; viral studies sent for atypical lymphocytosis and transaminitis; self-limiting symptoms, improved
10	29/F	No	Nausea, poor appetite, fatigue, hot flashes	…	Pos	Pos	…	Pos	Not detected	Pos	Pos	Not detected	No	Dual infection	Recently treated for Lyme; clinical improvement after 3 mo

Table 2. Continued

Pt ID	Age/ Sex	Immunocompromised	Presenting Symptoms and Signs	Heterophile Ab	EBV VCA IgM	EBV VCA IgG	EBV Early Ag, IgG	EBV EBNA, IgG	EBV DNA, IU/mL	CMV IgM	CMV IgG	CMV DNA, IU/mL	Follow-up Serology	Final Interpretation	Management/ Outcomes/Other Coexisting Illness
11	69/F	No	Fevers and malaise[a]	Neg	Pos	Pos	…	Pos	…	Pos	Pos	Not detected	No	Alternate diagnosis (false+ in the setting of anaplasmosis)[b]	Treated with doxycycline for anaplasmosis; self-limiting symptoms, improved
12	21/F	SLE on belimumab	None	Neg	Pos	Pos	…	Neg	Detected; 949	Pos	Pos	Not detected	CMV IgM in 1 wk (+) EBV DNA in 1 wk: undetectable	Acute EBV infection[b]	Viral studies sent for incidentally discovered atypical lymphocytosis after starting belimumab; patient later developed sore throat, eventually improved
13	30/F	No	Left upper quadrant abdominal pain, fevers, night sweats[a]	Neg	Pos	Pos	…	…	Detected; 127	Pos	Neg	Detected;1210 copies	CMV IgG in 4 wk (+) EBV DNA in 4 wk: 285	Acute CMV infection[b]	Viral studies sent for atypical lymphocytosis; course complicated by infected splenic infarct requiring drainage and IV antibiotics
14	24/F	No	Headaches, severe fatigue, fevers[a]	Neg	Pos	Pos	Pos	Pos	Not detected	Pos	Pos	Detected; <137	No	Acute EBV infection[b]	Viral studies sent for atypical lymphocytosis; symptoms improved during hospital stay
15	29/F	Crohn's disease on infliximab	Sore throat, fatigue, gastroenteritis, cervical lymphadenopathy[a]	…	Pos	Pos	Pos	Pos	Detected; <100	…	…	Neg	No	Acute EBV infection[b]	Diagnosed initially as recent EBV infection with necrotizing encephalitis (thalamic infarcts with negative LP) concerning for postinfectious inflammatory syndrome; long, complicated course, but recovered well
16	22/M	No	Headache, fatigue, nausea, sore throat, scleral icterus[a]	Pos	Pos	Pos	Pos	Neg	Detected; 844	Pos	…	Neg	No	Acute EBV infection	Course complicated by respiratory distress and hemolytic anemia requiring steroids
17	26/M	No	Nausea, fevers, abdominal pain, pelvic lymphadenopathy[a]	Pos	Pos	Pos	…	…	Detected; 1050	Pos	Neg	Neg	No	Acute EBV infection	Hospitalized with initial concern for heme malignancy with atypical lymphocytosis, thought to be acute EBV due to elevated viral load

Table 2. Continued

Pt ID	Age/ Sex	Immunocompromised	Presenting Symptoms and Signs	Heterophile Ab	EBV VCA IgM	EBV VCA IgG	EBV Early Ag, IgG	EBV EBNA, IgG	EBV DNA, IU/mL	CMV IgM	CMV IgG	CMV DNA, IU/mL	Follow-up Serology	Final Interpretation	Management/ Outcomes/Other Coexisting Illness
18	57/M	No	Fever, chills, night sweats, and myalgias[a]	Neg	Pos	Pos	…	…	Not detected	Pos	Pos	Detected;33 035	CMV IgM in 6 mo (–) CMV IgG in 6 mos (+)	Acute CMV infection[b]	Initial workup concerning for hematologic malignancy, but negative flow and viral testing with positive findings
19	50/M	No	Dyspnea, fatigue, weight loss, migratory arthralgias with new pericardial effusion[a]	…	Pos	Pos	…	…	Not detected	Pos	Pos	Neg	No	Alternate diagnosis (false+ in the setting of SLE)	Diagnosed with SLE by rheumatology during current admission
20	38/M	No	Cough, nightsweats, sore throat, myalgias, diarrhea, arthralgias	Neg	Pos	Pos	Pos	Pos	Not detected	Pos	Pos	Detected; 477	No	Acute CMV infection[b]	ID thought positive CMV IgM and viremia (even low level) consistent with primary CMV
21	26/M	Type 1 insulin-dependent diabetes	Fever, malaise, mild cough[a]	Neg	Pos	Pos	Neg	…	Not detected	Pos	Pos	Detected; 1354	No	Acute CMV infection	Was diagnosed outpatient with strep (positive testing) before hospital stay
22	19/M	No	No symptoms at time of lab test, elevated LFTs and atypical lymphocytosis on lab screen	Pos	Pos	Pos	Pos	Neg	Detected; 7440	Pos	Pos	Neg	No	Acute EBV infection	No further case details, follow-up closer to home with PCP
23	47/M	Psoriatric arthritis on secukinumab	Fever, cough, dyspnea, and diarrhea[a]	…	Pos	Pos	…	…	Detected; 4390	Pos	Neg	Detected; 55 572	CMV IgM in 5 d (+) CMV IgG in 5 d (+)	Acute CMV infection[b]	Admitted to the hospital with F&N; found to have CMV pneumonitis, started on ganciclovir, transitioned to valganciclovir, completing over a month of therapy once 2 viral loads were undetectable
24	40/F	No	Cough, fevers, fatigue, myalgias, cervical lymphadenopathy, trunk rash	Neg	Pos	Pos	…	Pos	Not detected	Pos	Neg	…	CMV IgM in 6 wk (–) CMV IgG in 6 wk (–)	Acute CMV infection[b]	Was being treated empirically with a 2-wk course of doxycycyline for Lyme disease (Lyme testing was eventually negative)
25	7/M	No	Headache, cervical lymphadenopathy, nasal congestion, cough, gastroenteritis	Neg	Pos	Pos	…	Neg	…	Pos	Neg	…	No	Dual infection	Clinically improved within a week with only some residual swollen lymph nodes

Table 2. Continued

Pt ID	Age/ Sex	Immunocompromised	Presenting Symptoms and Signs	Heterophile Ab	EBV VCA IgM	EBV VCA IgG	EBV Early Ag, IgG	EBV EBNA, IgG	EBV DNA, IU/mL	CMV IgM	CMV IgG	CMV DNA, IU/mL	Follow-up Serology	Final Interpretation	Management/ Outcomes/Other Coexisting Illness
26	4/M	No	Fever, headache, poor appetite, cervical lymphadenopathy, abdominal pain	…	Pos	Pos	…	Neg	…	Pos	Neg	…	No	Dual infection	PCP initially concerned about acute otitis media; patient failed to improve with a course of augmentin; re-presented with persistent fevers, found to have mono; recovered within a week
27	42/F	No	Headache, bilateral arthralgias, cervical lymphadenopathy, fatigue, low appetite	…	Pos	Neg	…	…	Not detected	Pos	Neg	Not detected	CMV IgM in 1 wk (–) CMV IgG in 4 wk (+) EBV IgM in 1 wk (–) EBV IgG in 4 wk (–)	Unclear[b]	Persistent symptoms for 3-4 wk; no therapy given, did end up resolving; ID thought this was an acute mononucleosis syndrome but was suspicious of *Bartonella* or toxoplasmosis with cat exposure (both serologies neg)
28	23/F	No	Sore throat, emesis, fever, jaundice, lymphadenopathy, abdominal pain	Neg	Pos	Pos	Pos	…	…	Pos	Pos	Not detected	No	Acute EBV infection[b]	Did not return after 2 wk of symptoms except to get labs, which showed improving LFTs and resolution of atypical lymphocytosis

Abbreviations: CHF, congestive heart failure; CMV, cytomegalovirus; EBNA, nuclear antigen; EBV, Epstein-Barr virus; F&N, febrile neutropenia; GCA, giant cell arteritis; ID, infectious diseases; IgG, immunoglobulin G; IgM, immunoglobulin M; ITP, idiopathic thrombocytopenic purpura; PCP, primary care physician; SLE, systemic lupus erythematosus; VCA, viral capsid antigen.

[a]Hospitalized.

[b]ID consulted.

aged 4–18 years, 11 aged 19–34 years, 11 aged 35–50 years, and 3 aged 51–73 years. Fifteen (54%) patients were men, and 14 (50%) required admission to the hospital. Sixteen (57%) patients had significant comorbidities, 7 of whom were immunocompromised. All patients were symptomatic at the time of testing; 13 (46%) of these patients had symptom onset <2 weeks prior. Eighteen (64%) had fever, chills, and malaise, 14 (50%) had atypical lymphocytosis, 9 (32%) had elevated liver function tests, 6 (21%) had lymphadenopathy, and 5 (18%) had splenomegaly. Six of 17 (35%) had positive heterophile antibody. Twenty-five of 27 (93%) had positive EBV IgG, 8 of 9 (89%) had positive EBV early antigen IgG, 8 of 15 (53%) had positive EBNA IgG, and 8 of 18 (44%) had detectable EBV PCR. Thirteen of 22 (59%) had positive CMV IgG, and 8 of 20 (40%) had detectable CMV PCR. Six (21%) had follow-up serologies ordered.

Table 2 presents a case summary with interpretation of dual positive serologies. Ten patients were diagnosed with acute EBV and 6 with acute CMV. For 4 patients, dual infection could not be excluded, and in 6 patients, the diagnosis remained unknown. Two patients had alternate diagnoses; anaplasmosis and systemic lupus erythematosus (SLE) were implicated to be the etiologies of the patients' clinical and laboratory presentations, with the positive EBV and CMV serologies being interpreted as false-positives. Six patients had follow-up serologies ordered ranging from 5 days to 6 months, with 3 of these follow-up tests assisting with the diagnosis. One patient died within 3 months of dual positive IgM test results. Further data on outcomes and duration of illness were unable to be uniformly obtained as many patients recovered and did not return for further follow-up.

DISCUSSION

In this review of patients testing positive for EBV IgM, simultaneously having a positive CMV IgM (dual positivity) was more common (~25%) than previously reported in the literature. True antigen cross-reactivity triggering these results is unlikely as the amino acid sequences of these orthologues are quite different. A more plausible explanation is that interfering substances (such as autoantibodies, heterophile antibodies, and serum binding proteins) can lead to false-positives [6]. The diversity of clinical characteristics of cases makes individual interpretation of positive and negative test results challenging.

There are no clear guidelines on how to interpret dual positivity for these 2 viruses. Hence, diagnosis should be established after taking the overall clinical context into consideration via case-by-case discussion. In more than half the cases, CMV and EBV viral load testing helped resolve the uncertainty when significantly elevated for one diagnosis compared with the other, suggesting that elevated viral loads may also reflect reactivation. EBV antinuclear IgG positivity was useful in context with other testing to demonstrate remote EBV infection. Repeating these serologies in 4–6 weeks can, in some cases, help ascertain the etiological agent of mononucleosis. In a minority of our cases, dual positivity was thought to represent false-positive results for both viruses when a separate infection occurred. In our population in the Northeast United States, we saw several cases where a recent tick-borne infection was the culprit, and with transaminitis in the setting of fever and other nonspecific symptoms, EBV/CMV was challenging to diagnose. Ultimately, in a sizeable proportion of our cases, the final diagnosis remained unknown. As obtaining the final diagnosis in patients with dual positivity can represent a significant challenge, clinicians must acknowledge the need for diagnostic stewardship and the potential for unneeded therapies at the time of ordering serologic testing.

Dual seropositivity for EBV and CMV IgM may be more common than previously reported. One possible explanation is that most of the patients in this predominantly hospital-based cohort were sicker and more complicated than those typically seen in outpatient clinical care. As there is no definitive diagnosis when both EBV and CMV IgM results are positive, clinicians should strongly consider supplemental testing (especially additional serologies and viral load assays) to resolve the diagnostic dilemma.

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