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Case Report

Central nervous system vasculitis from Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disorder in children: A case report

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Abstract

Background: Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disorders (EBV-T/NK-LPD) is a group of rare disorders resulting from EBV-infected T/NK-cells. It manifests as a broad spectrum of clinical symptoms according to immunologic status and viral load of an infected patient. Here, we report a boy who developed central nervous system (CNS) vasculitis and myelopathy as possible neurologic manifestations of EBV-T/NK-LPD.

Case report: A 16-year-old boy came to our hospital with a necrotic skin lesion on his right shoulder. He suffered from local skin reactions with high fevers after mosquito bites since he was 10 years old. During the evaluation of his skin lesion, he suddenly developed left facial palsy. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed acute infarctions of the pons and middle cerebellar peduncle and irregularities of both anterior inferior cerebellar arteries. Serologic testing showed an elevation of total Ig E levels, anti-VCA IgG levels, and anti-EA IgG titers. EBV DNA copy numbers of the whole blood and cerebrospinal fluid (CSF) were elevated. Biopsy of the right shoulder skin showed extranodal NK/T-cell lymphoma. According to clinical features and laboratory findings, he was diagnosed with EBV-T/NK-LPD. He was treated with chemotherapy and hematopoietic stem cell transplantation but developed recurrent infarctions during treatment.

Conclusion: This case showed the diagnostic challenge of neurologic manifestations of EBV-T/NK-LPD. EBV-T/NK-LPD-associated CNS vasculitis needs to be considered as a differential diagnosis of CNS vasculitis, when it is accompanied by the typical clinical spectrum of EBV-T/NK-LPD such as severe mosquito bite allergy, extranodal NK/T-cell lymphoma.

Keywords: Epstein-Barr virus; Vasculitis; Neurologic symptom; Lymphoproliferative disorder

1. Introduction

Epstein-Barr virus (EBV) is one of eight types of human herpesvirus types. EBV has been found to be ubiquitous in humans, with most humans infected

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during childhood through person-to-person contact such as saliva and genital secretions. Most EBV infections in children do not cause symptoms. However, EBV infection among adolescents and young adults may cause infectious mononucleosis whose clinical presentation consists of high fever, pharyngitis, lymphadenopathy, hepatomegaly, and splenomegaly. Furthermore EBV can cause various types of lymphoproliferative diseases, such as Burkitt lymphoma, Hodgkin's lymphoma, hemophagocytic lymphohistiocytosis, and non-lymphoid malignancies, such as nasopharyngeal carcinoma [1]. EBV-associated T/natural killer-cell lymphoproliferative disorders (EBV-T/NK-LPD) is a rare group of disorders characterized by clonal expansion of T cells or natural killer (NK) cells infected with EBV. With the accumulation of clinical data, it has been recognized that EBV-T/NK-LPD presents as a broad clinicopathologic spectrum depending on the immune response and EBV viral load of the infected patient [2].

EBV infection is also associated with neurologic disorders, with a reported incidence of 0.4–37.3%. These include meningitis, encephalitis, cerebellitis, transverse myelitis, cranial nerves paralysis, radiculopathies, Guillain-Barre syndrome, and sleep and behavioral abnormalities resulting from central nervous system (CNS) involvement [3]. However, most reported cases are related to primary EBV infection, and neurologic disorders associated with EBV-T/NK-LPD have been hardly reported. Here, we report a case of a patient who presented with EBV-T/NK-LPD-related neurological symptoms with extranodal NK/T-cell lymphoma and severe mosquito bite allergy (SMBA).

2. Case report

A 16-year-old boy was referred to our hospital for evaluation of a necrotic skin lesion on his right shoulder. He went to a dermatologic clinic before this because of a mass like lesion on the same area one month prior, and the mass was excised. After resection, the skin lesion developed necrotic changes and erythema. He was admitted to our hospital because the biopsy results showed markedly increased lymphocytic infiltration suggestive of lymphoma.

His perinatal and family histories were unremarkable. He suffered from local skin reactions with high fevers after mosquito bites since he was 10 years old. The skin lesions at mosquito bite sites changed into hemorrhagic bullae that subsequently developed into necrosis or an ulcer (Supplementary Fig. 1). He was diagnosed with Skeeter syndrome, a local allergic reaction caused by allergenic polypeptides in mosquito saliva.

One year before hospitalization, he came to our neurologic clinic due to a sudden onset of decreased pain and temperature sensations on his right upper and lower extremities and trunk. Other than that, he had no fever and other neurological symptoms. Spine magnetic resonance imaging (MRI) showed syrinx at T6-7 with subtle T2 hyperintensity changes at T5-9 level, but without enhancement (Fig. 1). His brain MRI and magnetic resonance angiography (MRA) were normal. Cerebrospinal fluid (CSF) analysis was normal except for elevated CSF leukocyte count (white blood cell count, 14 cells/μL; no red blood cells; glucose, 88 mg/dL; protein, 17 mg/dl; CSF IgG index, 0.08; oligoclonal bands, negative). CSF culture revealed no microorganisms. Immunologic evaluation for other autoimmune diseases was unremarkable. He was treated with systemic methylprednisolone, and his abnormal sensations were mostly improved without any changes on follow-up MRI.

Five days after the hospitalization, the patient suddenly felt dulled sensations on the left side of his face. He developed weakness in the same area, as well as horizontal nystagmus. On physical examination, he had splenomegaly. On blood examination, blood cell counts, electrolytes, and chemistry tests were all normal except for elevated serum total IgE levels up to 18,520 IU/mL. IgM antibodies to cytomegalovirus, EBV, human immunodeficiency virus, adenovirus, varicella zoster virus, herpes simplex virus, *Toxoplasma gondii*, and mycoplasma were all negative. CSF analysis, bacterial culture, and CSF cytology were all unremarkable. Brain MRI/MRA revealed high signal intensity on diffusion-weighted images with simultaneous low signal intensity on apparent diffusion coefficient maps in the left lateral pons and middle cerebellar peduncle and irregularities of both anterior inferior cerebellar arteries suggestive of acute infarction associated with vasculitis (Fig. 2).

Biopsy of the right arm skin lesion showed a polymorphic atypical lymphoid infiltration with cytotoxic T/NK cell lineage, mainly in the perivascular and periadnexal areas, and a positive signal for EBV-encoded small RNA (EBER) in situ hybridization. Immunochemistry showed positive results for Ki-67 (95%), CD3, CD56, TIA-1, and granzyme B, but a negative result for CD20. These results suggested extranodal NK/T-cell lymphoma in a background of chronic active EBV infection of NK-cell and T-cell type (Supplementary Fig. 2).

Since elevated serum IgE levels, SMBA, and the skin biopsy findings of NK/T-cell lymphoma were considered as clinical features of EBV-T/NK-LPD, we posited that the patient's neurological symptoms were related to EBV-T/NK-LPD. We therefore conducted further laboratory tests. Serology tests for EBV showed positive viral capsid antigen (VCA) IgG (556 IU/mL), early antigen (EA) DR IgG (82 IU/ml), and EBV nuclear antigen

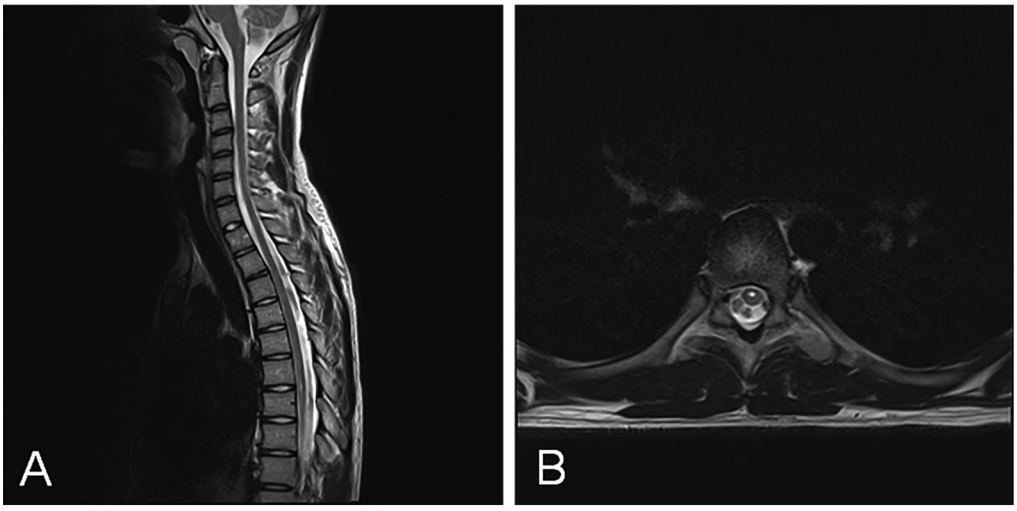

Fig. 1. Spine MRI taken a year before admission due to abnormal sensations. Sagittal (A) and axial (B) T2-weighted images revealed syrinx at the T6-7 level with subtle T2 hyperintensity at the T5-T9 level.

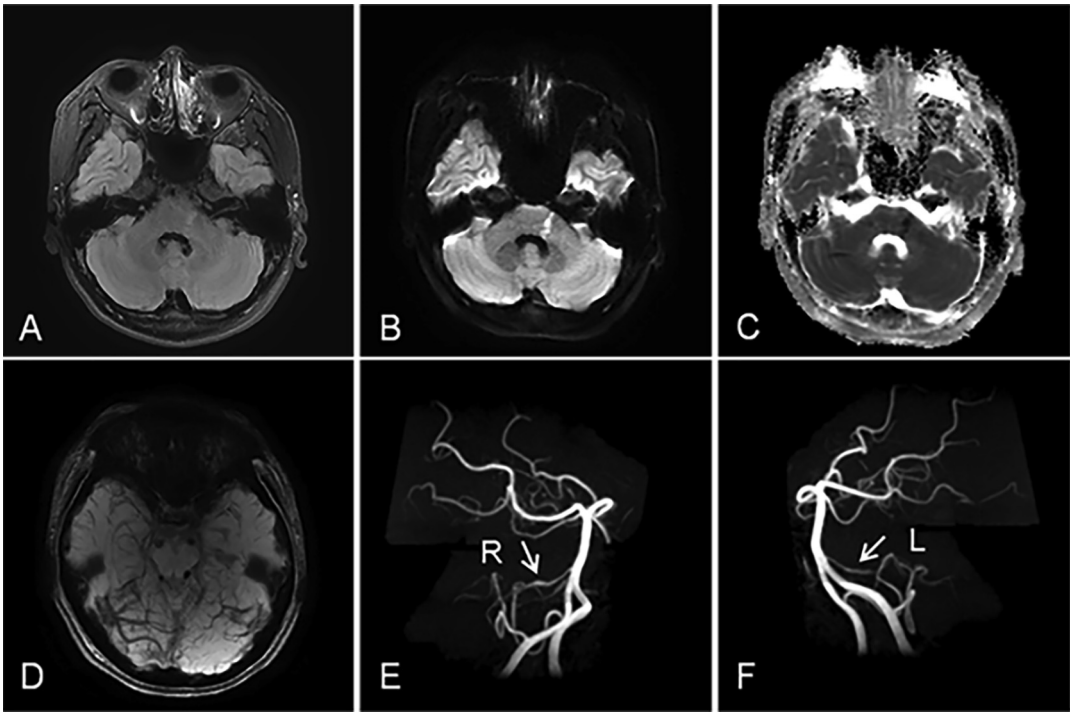

Fig. 2. Brain MRI and MRA showing neurologic complications associated with EBV-T/NK-LPD. (A) Axial FLAIR image demonstrated high signal intensity in left lateral pons. Simultaneously, diffusion weighted image showed high signal intensity (B) with low apparent diffusion coefficient values (C) in the same lesion, which was suggestive of acute infarction. (D) Susceptibility weighted imaging revealed multiple foci of hypo-intense signal in the both surface of midbrain, representing multiple small hemorrhage. (E, F) MRA demonstrated irregularities on both anterior inferior cerebellar arteries (AICA). White arrows indicate right AICA (E) and left AICA (F), respectively.

(EBNA) IgG (118 IU/ml), consistent with previous EBV infection. The EBV DNA copy number from the whole blood sample and CSF was 8.27×10^5 copies/mL and 5.10×10^3 copies/ml, respectively.

Based on these data and the clinical manifestations, the patient was diagnosed with EBV-T/NK-LPD with extranodal NK/T cell lymphoma, SMBA, and CNS vasculitis. He was treated with chemotherapy and underwent hematopoietic stem cell transplantation (HSCT). During the chemotherapy, he developed recurrent focal neurologic symptoms including headache, diplopia, dysarthria, and abnormal light reflex responses, caused by newly developed cerebral infarctions (Fig. 3). Since his catheter angiogram showed multifocal luminal ectasia

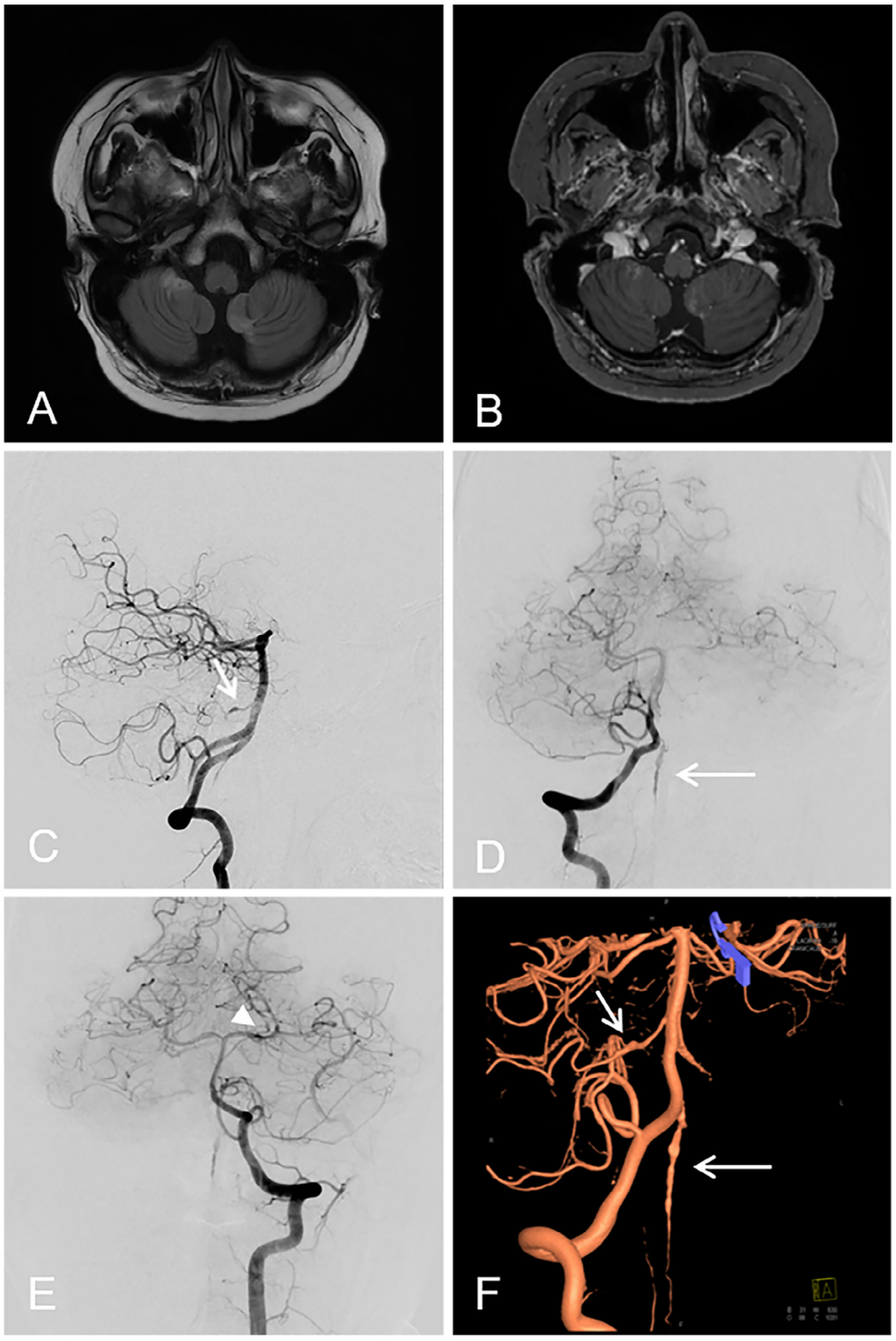

Fig. 3. MRI and catheter angiography performed for evaluation of recurrent neurological symptom in the course of treatment. Brain MRI performed due to a sustained headache showed new T2/FLAIR hyperintensity in the bilateral inferior cerebellum (A, B) and the right lateral medulla (now shown in this image) with irregular enhancement. Catheter angiograms (C, D, E) and their three-dimensional reconstruction (F) revealed multifocal luminal ectasia in anterior spinal artery (long arrow), right anterior inferior cerebellar artery (short arrow) and left posterior cerebral artery (arrowhead).

in the anterior spinal artery, right anterior inferior cerebellar artery, and left posterior cerebral artery, he was started on aspirin treatment. Nevertheless, the patient maintained the compete response status for 6 months after HSCT without any remaining neurological complications.

3. Discussion

Our case illustrated the diagnostic challenges of EBV-T/NK-LPD and related neurologic complications, including myelopathy and CNS vasculitis. EBV-T/NK-LPD is a rare EBV-associated lymphoproliferative disorder with a broad spectrum of clinical presentations. The incidence of the T/NK-cell type of this disease varies markedly by race, with most cases occurring in East Asians [2]. Although multiple facets of this disease are not fully understood, EBV-T/NK-LPD is classified as four diseases according to the 2017 World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues. These types include systemic EBV-positive T-cell lymphoma of childhood, systemic form of chronic active EBV infection (CAEBV) of T/NK-cell type, hydroa vacciniforme-like lymphoproliferative disorder, and SMBA [4]. Extranodal NK/T-cell lymphoma is also classified under the umbrella of EBV positive T-NK cell proliferations. The diagnostic criteria of CAEBV include infectious mononucleosis-like symptoms persisting for more than 3 months, increased EBV DNA content ($>10^{2.5}$ copies/μg DNA) in the peripheral blood, histological evidence of organ disease, and demonstration of EBV RNA or viral protein in the affected tissues of patients without a known immunodeficiency, malignancy, or autoimmune disorder [4]. Although this case does not fulfill the criteria for CAEBV because of the absence of infectious mononucleosis-like symptoms, it can be considered on the continuous spectrum of CAEBV. EBV-T/NK-LPD can vary on a clinical spectrum in the same patient, with one patient's disease evolving into other types of EBV-T/NK-LPD, as in our case.

SMBA is a cutaneous manifestation of EBV-T/NK-LPD, characterized by abnormally intense local reactions including erythema, bullae, ulcers, and scar formation [2]. SMBA may be accompanied by high titers of IgE antibody and systemic symptoms such as fever, lymphadenopathy, and liver dysfunction after mosquito bites [5]. In our case, the patient had been misdiagnosed with Skeeter syndrome, caused by allergenic polypeptides in mosquito saliva, before coming to our hospital. With laboratory findings including high EBV DNA copy numbers from a blood sample, high titers of IgE, positive immunologic tests for EBV, and positive EBER in situ hybridization in the skin biopsy, a local skin reaction after a mosquito bite could be diagnosed as SMBA. The classic appearance of the skin lesion allowed us to conclude that the patient's unexplainable neurologic symptoms could be related to EBV-T/NK-LPD.

The patient presented with myelopathy and recurrent cerebral infarctions caused by CNS vasculitis. We excluded various disorders from our differential that might lead to these neurologic symptoms, such as autoimmune disease, fungal infection, and other viral infections. To date, neurologic manifestations of EBV-T/NK-LPD have rarely been reported [6–8]. Previous studies have reported rare cases of EBV-T/NK-LPD showing extensive CNS involvement, acute disseminated encephalomyelitis, brain atrophy, and myelopathy with poor prognosis. Kobayashi et al. reported an autopsy case of CAEBV showing perivascular CD3+ and EBER1+ lymphocyte infiltration with multiple necrotic foci in an extensive CNS lesion [6]. This findings can be related to the mechanism of CNS vasculitis in our case. Other autopsy cases have described EBV-associated CNS vasculitis in an immunocompromised state due to medications or human immunodeficiency virus infection [9,10]. These cases indicated that EBV-associated vasculitis should be considered as a differential diagnosis of CNS vasculitis.

In conclusion, we report a rare neurologic complication related to EBV-T/NK-LPD presenting as myelopathy and CNS vasculitis, especially in children. A neurologic disorder associated with EBV-T/NK-LPD should be considered when the clinical spectrums of EBV-T/NK-LPD, such as SMBA and extranodal NK/T-cell lymphoma, accompany the patient's symptoms.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.05.009.

References

[1] Straus SE, Cohen JI, Tosato G, Meier J. Epstein-Barr virus infections: biology, pathogenesis, and management. Ann Intern Med 1993;118:45–58.
[2] Kimura H, Fujiwara S. Overview of EBV-associated T/NK-cell lymphoproliferative diseases. Front Pediatr 2018;6:417.
[3] Mazur-Melewska K, Brenska I, Jonczyk-Potoczna K, Kemnitz P, Pieczonka-Ruszkowska I, Mania A, et al. Neurologic complications caused by Epstein-Barr virus in pediatric patients. J Child Neurol 2016;31:700–8.
[4] Quintanilla-Martinez L, Ko Y-H, Kimura H, Jaffe ES. EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: WHO IARC Press; 2017. p. 355–62.
[5] Ishihara S, Ohshima K, Tokura Y, Yabuta R, Imaishi H, Wakiguchi H, et al. Hypersensitivity to mosquito bites conceals clonal lymphoproliferation of Epstein-Barr viral DNA-positive natural killer cells. Jpn J Cancer Res 1997;88:82–7.
[6] Kobayashi Z, Tsuchiya K, Takahashi M, Yokota O, Sasaki A, Bhunchet E, et al. An autopsy case of chronic active Epstein-Barr virus infection (CAEBV): distribution of central nervous system (CNS) lesions. J Neurol Sci 2008;275:170–7.
[7] Ohga S, Takada H, Honda K, Inamura T, Gondo K, Ohshima K, et al. Central nervous system T-cell lymphoproliferative disorder in a patient with chronic active Epstein-Barr virus infection. J Pediatr Hematol Oncol 1999;21:42–6.

[8] Shoji H, Kusuhara T, Honda Y, Hino H, Kojima K, Abe T, et al. Relapsing acute disseminated encephalomyelitis associated with chronic Epstein-Barr virus infection: MRI findings. Neuroradiology 1992;34:340–2.

[9] Kano K, Katayama T, Takeguchi S, Asanome A, Takahashi K, Saito T, et al. Biopsy-proven case of Epstein-Barr virus (EBV)-associated vasculitis of the central nervous system. Neuropathology 2017;37:259–64.

[10] Raman L, Nelson M. Cerebral vasculitis and encephalitis due to Epstein-Barr virus in a patient with newly diagnosed HIV infection. J Clin Virol 2014;59:264–7.