Case Report

Infective Endocarditis Following Chicken Pox: A Rare Association

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Summary: A 38-year old immunocompetent male presented to us with chicken pox complicated by development of Guillain-Barre syndrome (GBS) and left-sided native valve endocarditis due to methicillin resistant *Staphylococcus aureus* (MRSA). This was further complicated by embolization to various vital organs including the brain. The patient was treated with vancomycin for four weeks but did not respond to the treatment. We present this case to highlight the rare complications associated with chicken pox and the challenges faced in management of such a case.

Key words Guillain-Barre syndrome, Methicillin resistant *Staphylococcus aureus*, Varicella zoster

INTRODUCTION

Chicken pox is a relatively benign disease in childhood caused by varicella zoster virus (VZV). Complications may develop in a small percentage of cases. This percentage is higher in adults, especially in the immunosuppressed. Guillain-Barre syndrome (GBS) is a peripheral neuropathy in which an infection or vaccination leads to a misdirected immune response against the myelin sheath and axons of neurons. GBS following chicken pox has been rarely described in the published literature [1]. Cardiac complications of chicken pox are extremely unusual, but directly or indirectly may lead to pericarditis, myocarditis and endocarditis [2]. Endocarditis complicating varicella is usually seen with *Streptococcus* spp or *Staphylococcus* spp. The exact mechanisms by which VZV predisposes the individual to secondary bacterial endocarditis remain unclear. Proposed hypotheses range from bacterial superinfection of skin lesions to transient suppression of dendritic cell func-

tions [3]. We present the case of a 38-year old immunocompetent male with extremely rare complications associated with chicken pox and discuss the challenges faced in the management of such cases.

CASE REPORT

A 38-year-old male, with no prior comorbidities or addictions, presented with a history of high-grade fever associated with chills and myalgia for eight days and vesicular skin rash for four days, which started on the trunk and spread to the extremities. Two days following the rash, he developed sudden onset symmetrical weakness of the lower limbs (proximal>distal), which progressed to involve the upper limbs one day later. There was no history suggestive of bowel or bladder involvement. There was no history suggestive of any sensory or cranial nerve involvement, dog-bite, recent vaccination. The patient had been evaluated at a different hospital prior to visiting our institute. Routine hematology and biochemistry showed mild leuko-

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Abbreviations: AMSAN, acute motor sensory axonal neuropathy; CNS, Central Nervous System; CSF, cerebrospinal fluid; GBS, Guillain-Barre syndrome; IDSA, Infectious Diseases Society of America; MRI, Magnetic resonance imaging; MRSA, methicillin resistant *Staphylococcus aureus*; TDM, Therapeutic Drug Monitoring; VZV, varicella zoster virus;

cytosis, thrombocytopenia and transaminitis (Table 1). Cultures and two dimensional echocardiography (2D echo) were non-contributory (Table 1).

On examination, the patient was conscious and oriented. He was febrile (38.3–38.4 degree Celsius) with stable vitals (heart rate- 106/min, blood pressure- 118/76 mm of Hg). On general physical examination, pallor was present with erythematous vesicular rashes at multiple stages of development over the trunk and limbs. Detailed neurological examination showed Grade 0/5 hypotonia in all four limbs. Deep tendon reflexes were absent and plantars were equivocal bilaterally. Bilateral lower motor neuron type facial palsy was present. Meningeal signs were absent. Other systematic results were normal.

Routine hematological and biochemical parameters were non-contributory (Table 1). A cerebrospinal fluid (CSF) analysis revealed a total cell count of 170/ μ L with lymphocytic predominance. CSF protein was high (168 mg/dL) but the sugar level was only 60 mg/dL (simultaneous blood sugar levels were 124 mg/dL). CSF analysis for tuberculosis by cartridge based nucleic acid amplification test was negative, as were polymerase chain reaction assay for herpes simplex

virus and cryptococcal antigen. Bacterial and fungal cultures of CSF were sterile. A nerve conduction study indicated acute sensory-motor polyneuropathy, suggestive of AMSAN type GBS. The patient was started on intravenous immunoglobulin and injectable (intravenous) acyclovir, based on a working diagnosis of Guillain-Barre syndrome secondary to chicken pox.

Two days into the admission, the patient developed progressive worsening of sensorium. Magnetic resonance imaging (MRI) of the brain showed multiple diffuse punctate hemorrhages in the cortical and subcortical areas (Figure 1). A focal hyper-intensity was noted in the right occipital area on diffusion weighted image. We suspected varicella encephalitis, so intravenous pulse steroid was given at a dose of one gram for five days, but the fever spikes persisted. A new onset pan systolic murmur was heard in the mitral area on daily rounds. 2D echocardiography done at that time showed a 5×8 mm vegetation in the posterior mitral valve. Blood was sent for aerobic, anaerobic and fungal cultures. The patient was started empirically on vancomycin (1 gram twice daily) and gentamicin (80 milligrams thrice daily).

On day seven of the therapy his fever spikes re-

TABLE 1.
Laboratory parameters of the patient before admission, on admission and after four weeks of admission

	Outside hospital	On Admission	After 4 weeks
Hb (g/dL)	9.1	8.9	7.8
TLC (/mm ³)	11330	9200	10800
Platelet count (/mm ³)	67000	1,22,000	1,15,000
DLC	Neutrophils (64%), Lymphocyte (31%)	Neutrophils (70%), Lymphocyte (24%)	Neutrophils (74%), Lymphocyte (22%)
Urea(mg/dL)	56	88	52
Creatinine(mg/dL)	1.2	1.6	0.8
Calcium (mg/dL)	8.4	8.1	8.2
Phosphate (mg/dL)	2.8	2.4	2.5
Sodium(mEq/L)	141	132	138
Potassium(mEq/L)	4.2	3.1	3.1
Bilirubin (mg/dL)	0.8	0.2	0.4
Total Protein (g/dL)	6.1	5.8	6.3
Albumin (g/dL)	1.9	1.6	2.2
SGOT(IU/L)	47	83	87
SGPT(IU/L)	62	67	78
ALP(IU/L)	82	90	386

duced. By that time, peripheral signs of infective endocarditis (Splinter hemorrhages and Janeway lesions) had started to appear (Figure 2). Two blood cultures were positive for Methicillin Resistant *Staphylococcus aureus* (MRSA) sensitive to vancomycin. Gentamicin was discontinued at this time. He had started to recover power in his limbs (Grade 2/5). Repeat blood cultures were sterile. A repeat MRI of the brain was planned after four weeks of therapy to assess the response. Repeat MRI revealed development of new onset hyper intensity in the left temporo-parietal region with localized meningeal enhancement (Figure 3). There was significant resolution, however, in the previous occipital lesion. Repeat CSF was unremarkable. The vancomycin dose was increased to 1 gm thrice daily and rifampicin was added. A repeat 2 D

echocardiography was performed which was suggestive of an increase in the size of vegetations in the mitral valve (11×15 mm). A bed side abdomen ultrasound was done which was suggestive of a 3×4 cm organized abscess in the spleen. The serum vancomycin (41 µg/ml) and CSF vancomycin (4 µg/ml) levels were estimated using liquid chromatography and mass spectroscopy (Figure 4). Vancomycin was replaced with high dose daptomycin (10 mg per kg). The daptomycin levels in serum and CSF were found to be 15.27 µg/ml and 0.42 µg/ml respectively (Figure 5). An urgent cardio-thoracic surgery consultation was taken and the patient was planned for surgery. However, he developed sudden onset altered sensorium with hypotension and hematuria. The patient was started on vasopressors and shifted to intensive care but he suc-

Fig. 1. MRI brain (A): Post gadolinium contrast of MRI brain image showing well defined occipital hyper-intensity at admission (B) Post gadolinium contrast of MRI brain image showing new hyper-intensity in the left temporo-parietal area with surrounding leptomeningeal enhancement.

Fig. 2. A) Clubbing with splinter haemorrhages B) Jane way lesions in lower limbs.

cumbed to refractory shock.

DISCUSSION

VZV is known to increase the risk of GBS in patients with herpes zoster however, reports of GBS following chicken pox are extremely rare. In an analysis done by Cresswell *et al.*, out of 50 cases of GBS after VZV infection, six patients had GBS following chicken pox [4]. The usual time period between chicken pox and GBS was around two weeks to two months. Shorter time to onset was associated with greater severity [4]. A similar observation was made in our case.

Encephalitis is not an uncommon complication of varicella infection. It usually manifests one week into the course of illness but may also precede the vesicular rash in some cases [5]. In children, acute cerebellar ataxia is more commonly seen while diffuse encephalitis is more common in adults [5]. Patients with diffuse encephalitis usually present with altered sensorium with or without seizures and focal neurological deficit [5]. Imaging may reveal nonspecific infarcts/

hemorrhages suggesting vasculopathy of small, medium or large vessels [6]. In this patient, an initial diagnosis of varicella encephalitis was made, but in hindsight the findings were more consistent with septic emboli due to infective endocarditis.

Infective endocarditis, in general, may be associated with various systemic complications. Septic embolism to vital organs including brain may be seen in up to one-fourth of the cases [7]. Risk of embolic events are higher with *Staphylococcus* spp infection, along with vegetations on mitral valves and vegetation size of >10 mm [7]. Patients with infective endocarditis associated with *Staphylococcus aureus* have persistent bacteremia, are difficult to treat and are more likely to have poor outcomes [8]. The mortality increases further if there is methicillin resistance or if the left side of the heart is involved [8].

Vancomycin is the drug of choice for MRSA endocarditis according to most international associations [9]. Therapeutic drug monitoring of vancomycin is helpful in patients with inadequate response. For effective treatment of MRSA endocarditis, target trough

Fig. 3. MRI Brain (A) T2 weighted image suggestive of hyper-intensity in occipital region at admission (B) T2 weighted image suggestive of resolution of hyper-intensity in occipital region and new hyper-intensity in the left temporo-parietal region (C&D). Diffusion weighted image suggestive of multiple micro haemorrhages in cortical and subcortical area at admission (C) and later (D).

concentration of vancomycin should be 15–20 ng/ml. Close monitoring of vancomycin trough concentrations and dosing adjustment has been shown to result in improved patient outcomes. Vancomycin has poor CNS penetration in uninflamed meninges and therefore, TDM in CSF seems to be rational. Unfortunately,

ideal trough concentration in CSF for septic emboli in the brain is not known. However, a corollary can be drawn from the recommended CSF trough concentration of $>5 \mu\text{g/ml}$ in ventriculoperitoneal shunt infections [10]. In this case, vancomycin levels were higher than the target trough concentration in the serum. With

Fig. 4. Representative liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) chromatograms of vancomycin resulting from analysis of (A1) blank cerebrospinal fluid, (A2) 50-fold diluted cerebrospinal fluid, (B1) blank serum and (B2) 500-fold diluted serum.

Fig. 5. Representative LC-ESI-MRM chromatograms of daptomycin resulting from analysis of (A1) blank Cerebrospinal fluid, (A2) 50-fold diluted cerebrospinal fluid, (B1) blank serum and (B2) 500-fold diluted serum.

a penetration of around 10%, the CSF levels were also probably close to the target trough concentration. However, poor clinical and radiological response, even after more than four weeks of therapy, prompted us to make a diagnosis of vancomycin failure. This may have been because of poor drug penetration into vegetations/ bacterial biofilms or because of the high bacterial densities that effect the antimicrobial activity of glycopeptides. It must also be noted that prolonged administration of vancomycin for over four weeks may result in a more pronounced reduction in systematic clearance of vancomycin than creatinine clearance and therefore, serum concentration may be higher than desired [11].

In cases where there is no response after achieving adequate trough concentrations, surgical intervention or use of alternatives to vancomycin are the only options. Daptomycin may be a reasonable alternative to vancomycin for MRSA native valve endocarditis [9]. In an open-label randomized controlled trial by Fowler *et al.*, daptomycin was found to be non-inferior to vancomycin in patients with right sided MRSA endocarditis [12]. Smaller human studies for left sided endocarditis have shown daptomycin to be equally effective [13]. The *in vitro* and *in vivo* efficacies of daptomycin vs vancomycin against MRSA clinical isolates have been studied in a rabbit model of infective endocarditis. Daptomycin was significantly more effective than vancomycin in reducing the density of bacteria in the vegetations [14]. Higher doses of daptomycin has been tried in CNS infection with considerable success. Daptomycin may have a slightly better penetration in noninflamed meninges than vancomycin according to animal studies [15]. However, the target trough concentration of daptomycin in serum and CSF has not been well established. The patient was switched over to daptomycin owing to the poor response to vancomycin and theoretical non-inferiority of daptomycin in such conditions. However, the CSF penetration of daptomycin was found to be only 2.75%. The prognosis of MRSA bacteremia causing infective endocarditis is known to be poor, and our patient succumbed to his illness before any further actions could be taken. IDSA guidelines recommend valve surgery in cases of native valve infective endocarditis with large vegetations (greater than 10 mm in diameter), occurrence of one or more embolic events during the first two weeks of therapy, severe valvular insufficiency, valvular perforation or dehiscence, decompensated heart failure, perivalvular or myocardial abscess, or new heart block [16].

This case demonstrates the unusual association of

chicken pox with GBS and infective endocarditis. It also points out the difficulties faced during management of MRSA infective endocarditis with possible septic embolism to brain. We report this case to highlight the possible use of early therapeutic drug monitoring in overcoming these difficulties. Further research is needed to standardize the target concentration of these drugs at various dosages in different body fluids.

LEARNING POINTS

1. Herpes zoster is commonly known to predispose to Guillain Barre syndrome. Similar predisposition can be seen in chicken pox, although rarely. Chicken pox can also predispose to infective endocarditis.
2. Patients with infective endocarditis with Methicillin Resistant *Staphylococcus aureus* (MRSA) have persistent bacteremia, are difficult to treat and are more likely to have poor outcomes.
3. Vancomycin is the drug of choice of MRSA endocarditis but in unresponsive cases daptomycin can be used. Therapeutic drug monitoring of vancomycin and daptomycin may be useful in decision making in such patients.

CONFLICT OF INTEREST: None

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