ORIGINAL RESEARCH PAPER | Medicine | Volume - 7 | Issue - 4 | April-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

ATYPICAL VARICELLA ZOSTER INFECTION WITH SECONDARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SYNDROME: A CASE REPORT

KEYWORDS: Atypical Varicella Infection, Complications, Adult Chickenpox, Haemophagocytic Lymphohistiocytosis

Dr. Angeline Sophia Rajakumar
M.B.B.S, Undergraduate, Sri Ramachandra medical college and research institute

Dr. Madhavan K.
Associate Professor and Unit Chief, Department of General Medicine, Sri Ramachandra medical college and research institute

Dr, Priyadarshini V.
Assistant Professor, Department of General Medicine, Sri Ramachandra medical college and research institute

Dr. Nandini Ravi
M.D, Postgraduate, Department of General Medicine, Sri Ramachandra medical college and research institute

ABSTRACT Chicken pox is caused by varicella zoster virus (VZV) which is a dermatotropic and neurotrophic virus that usually produces primary infection in childhood. The disease in children is usually well-tolerated. Manifestations are more severe in adults, pregnant women and immunocompromised. Clinical symptoms of VZV infection include fever with rashes progressing from small pink macules to vesicles and pustules in a centripetal distribution, with fresh crops every 2–4days. Atypical manifestations include pneumonitis, hepatitis, encephalitis and cerebellitis. The following case describes a patient with VZV infection presenting with fever, rashes, abdominal pain and history of giddiness and swaying on walking. Patient developed secondary haemophagocytic lymphohystiocytosis syndrome (HLH), which is a rare complication. after 4 days and was managed symptomatically. This case is atypical in terms of the rapidity of clinical deterioration and multi organ systems involvement along with secondary HLH.

INTRODUCTION

The present case report describes a case of atypical varicella zoster infection with secondary haemophagocytic lymphohystiocytosis syndrome. Clinical manifestations, complications and prevention are discussed. This article is to enlighten that complications of varicella zoster infection and HLH secondary to VZV infection in adults can be life-threatening even in immunocompetent individuals. The intention is to remind clinicians that although varicella is most often a relatively benign and self-limiting childhood illness, the disease can be associated with a variety of serious and potentially lethal complications in both immunocompromised and immunocompetent individuals.

CASE PRESENTATION

A 27-year-old previously healthy female with a contact history of chicken pox from her younger brother was brought to our emergency department on November 2016 with alleged history of fever for 2 days, which was high grade and associated with chills and rigors and complaints of rashes all over the body. Patient had complaints of abdominal pain for 2 days, pricking type of pain, in the epigastric region. Patient also gave a history of loose stools, 2-3 episodes for 1 day. Patient had complaints of easy fatigability and generalised myalgia. Patient also gave a history of swaying while sitting and walking along with difficulty in manoeuvring food from plate to mouth for 1 day.

On arrival to the emergency, patient was conscious and oriented. Her blood pressure was 130/80 mm Hg, with pulse rate of 130/min, respiratory rate of 20/min. She was afebrile and her room air saturation was 100%. Patient had jaundice and pleomorphic skin rashes (macules, papules, pustules and vesicles) with no scabs present all over the body sparing the palms and soles. Systemic examination revealed bilateral cerebellar signs, no signs of meningitis and mild epigastric tenderness with no organomegaly.

FIGURE 1

INVESTIGATIONS DONE ON DAY OF ADMISSION

Complete Blood Count:
Haemoglobin - 12.6
Platelets - 1.05
Total Count - 2400

Arterial Blood Gases:
pH – 7.569
pCO2 – 19 mm Hg
pO2 – 76 mm Hg

Urine Routine:
Glucose – 2+
Protein – 2+
Pus cells – 6 - 8

HIV: Non-reactive
USG Abdomen: Mild ascites
ECG: Sinus Tachycardia
Cardiac Markers: Mildly Positive
Dengue NS1 Antigen and Dengue Serology: Negative
Malarial Antigen: Negative
Leptospirosis: Negative for IGM antibodies
QBC for MP and MF: Negative
All **Routine Blood Investigations** given in Table 1

units of platelets were transfused on the first day. Patient was diagnosed to have varizella zoster infection with complications of cerebellitis and probable myocarditis. Patient was initially treated with Inj. Acyclovir 500 mg i.v TDS, Inj. Ceftriaxone 2gm i.v BD, IV Fluids and other supportive measures.

On day 2, patient developed altered sensorium. MRI brain was done and found to be normal. Lumbar puncture was planned but deferred in view of thrombocytopenia. 2D Echo done revealed normal chamber dimensions, no wall motion abnormality, and ejection fraction = 64%. Repeat Trop T was also negative. Hence, myocarditis was ruled out but patient continued to have persistent fever spikes. On 29/11/2016, repeat investigations revealed Hb of 5.4, total count of 800, platelet of 81,000, INR - 1.16, with RFT and serum electrolytes within normal limits. In view of the patient's condition, a suspicion of probable haemophagocytic lymphohistiocytosis syndrome was made. Serum ferritin and triglycerides were elevated. Haematology opinion was obtained and patient was diagnosed to have HLH and treated accordingly. Antibiotics were stepped up to Inj. Meropenem and Inj. Amikacin in view of neutropenic sepsis with serum procalcitonin >100.

Volume - 7 | Issue - 4 | April-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

On 30/11/2016, patient developed tachypnoea and tachycardia with complaints of breathlessness. Patient was intubated and was on mechanical ventilation on pressure control mode. CBC was monitored daily and platelets were found to be persistently dropping to a lowest of 21,000. Patient was transfused with multiple units of platelets, fresh frozen plasma and packed cells as and when required based on daily monitoring. On 03/12/2016, repeat investigations revealed pancytopenia and deranged bicarbonate value as shown below in TABLE 1. On the same day, around 08:00 P.M, patient had profuse ET tube bleed with ET block. Hence, patient was extubated and re-intubated. Despite mechanical ventillation, patient had persistent hypoxia. Repeat chest X-ray showed diffuse infiltration in the right hemithorax with left upper lobe opacities (IMAGE 2). Pulmonologist reviewed the patient and planned for bronchoscopy but the procedure was deferred in view of the patient's poor haemodynamic status. Patient developed sudden cardiac arrest. Patient was revived according to ACLS protocol and continued on ventilatory and inotropic support. 12 units of platelets were transfused along with 2 units of paced cells and 4 units of fresh frozen plasma. On the same day, patient developed oliguria. Nephrology opinion was obtained in view of oliguric AKI and patient was advised lasix infusion with i.v fluids at 50 ml/hr.

On 04/12/2016, patient had nil urine output. Labs revealed deranged Renal Function Test values and Serum Electrolytes as shown below in TABLE 1. Acyclovir and Amikacin were withheld in view of AKI . Nephrology opinion was obtained and patient was planned for haemodialysis. In view of hypotension, patient was planned for Continuous Renal Relacement Therapy instead of Haemodialysis. On 05/12/2016, at 4:30 a.m, patient went into asystole. Patient was resuscitated according to ACLS protocol. Inspite of all efforts, patient could not be revived and succumbed to the disease at 06:56 a.m on 05/12/2016.

DATE LABS	26/11/2016	27/11/2016	28/11/2016	29/11/2016	30/11/2016	01/12/2016	02/12/2016	03/12/2016	04/12/2016	05/12/2016	BIOLOGICAL REFERENCE INTERVAL
Haemoglobin (gms/dl)	12.6			5.4	8.2 9.1	8.7	8.2	7.9	7.7 7.4	6.9	12.0 — 15.0
Platelets (lakh/cumm)	1.05	0.90	0.66	0.81	1.05 (MC) 0.36	0.45	0.21	0.22	1.10 1.22	0.22	1.5 — 4.5
Total Count (cells/cumm)	2400			800	1100 1500	1500	1300	1200	600 700	600	4000 - 11000
PT (sec)	22.4		16.3	14.2	11.8	12.5			19.0	28.4	11 — 16
Control	12.3		12.3	12.3	12.3	12.3			12.3	12.3	
PTT (sec)	55.9			31.8		29.1			32.2		27 — 40
Control	30.0			30.0		30.0			30.0		
INR	1.89		1.35	1.16	0.96	1.02			1.59	2.43	
BUN (mg/dl)	10			8	12	13		9	35	45	5 — 21
CREATININE (mg/dl)	0.6			0.5	0.5	0.6		0.4	2.2	3.5	0.6 — 1.10
SODIUM (mmol/L)	122	130	136	137	134	132		133	155 139	148	132 — 146
POTASSIUM (mmol/L)	4.2	3.7	3.7	4.0	3.3	3.5		3.9	5.2 5.5	5.7	3.50 — 5.00
CHLORIDE (mmol/L)	94	103	110	110	106	104		106	105 107	102	96 — 108
BICARB (mmol/L)	13	15	16	15	11	15		19	20 11	16	22 — 29
SGOT (U/L)	393			199			131		328	3350	<40
SGPT (U/L)	399			126			75		97	570	<41
ALKALINE PHOSPHATE (U/L)	134			77			248		168	193	45 — 129
TOTAL BILIRUBIN (mg/dl)	2.69			3.60			3.81		5.26	9.14	0.1 — 1.0
DIRECT BILIRUBIN (mg/dl)	1.89			2.71			3.25		4.22	6.45	0.0 — <0.2
FERRITIN (ng/ml)			3587.4	5298.7							10 — 291

Values HIGHER than the normal range are highlighted in RED
Values LOWER than the normal range are highlighted in BLUE
Split cells reveal morning results in upper slot and evening results in lower slot.
MC = Manually Counted

TABLE 1: LABORATORY INVESTIGATIONS OF THE PATIENT

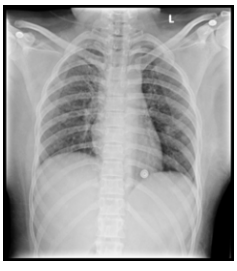

IMAGE 1 Chest X-ray of the patient taken on 26/11/2016.

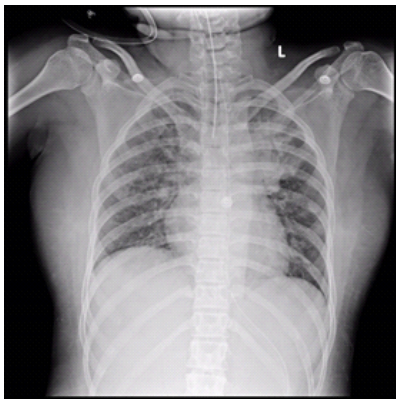

IMAGE 2 Chest X-ray of the patient taken on 30/11/2016.

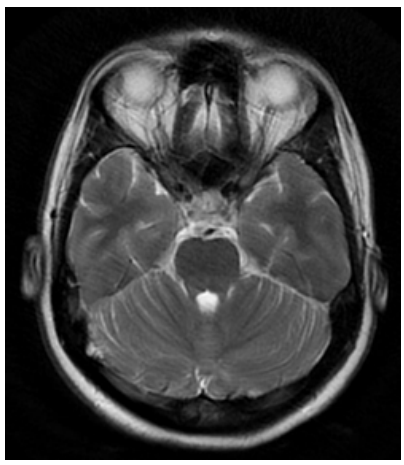

IMAGE 3: MRI Brain of the patient revealing Normal Study.

DISCUSSION

Varicella zoster is a DNA virus belonging to the family of Herpes viridae. The attack rate for varicella is approximately 90% in susceptible individuals. [1] Disease in children is usually well tolerated. Manifestations are more severe in adults, pregnant women and the immunocompromised with severe rashes and visceral involvement. [2]

Prior to the introduction of varicella vaccination, the fatality rates for varicella were approximately 1 per 100,000 cases among children 1-14 years of age, 2.7 per 100,000 cases among persons 15-19 years of age, and 25.2 per 100,000 cases among adults 30-49 years of age. Adults accounted for only 5% of reported cases of varicella but approximately 35% of mortality. According to CDC, groups at increased risk of complications include - persons older than 15 year of age, infants younger than 1 year of age, immunocompromised and newborns of women with rash onset within 5 days to 2 days after delivery. [3] Our patient was a healthy 27-year-old healthy immunocompetent female with fulminant varicella infection, multi system dysfunction and secondary haemophagocytic lymphohistiocytosis syndrome.

The typical clinical presentations of varicella and herpes zoster are distinctive and readily recognized by most experienced clinicians. However, atypical clinical presentations and uncommon complications of these diseases can pose diagnostic and therapeutic challenges. The most common infectious complication of varicella is secondary bacterial superinfection of the skin Most often by staphylococcus or streptococcus species. The most common extra cutaneous site of involvement is CNS - acute cerebellar ataxia, aseptic meningitis and encephalitis. Transverse myelitis, Guillain-Barré syndrome and Reye's syndrome can also occur. Varicella

Volume - 7 | Issue - 4 | April-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

pneumonia is the most serious complication following varicella infection, developing more commonly in adults (upto 20% of cases) than in children. Other rare complications include myocarditis, corneal involvement, arthritis, bleeding diathesis, acute glomerulonephritis and hepatitis. [4]

Pneumonitis is rare in healthy children but occurs with increased frequency in immunocompromised persons of all ages and in immunocompetent adolescents and adults. 2.7%–16.3% will have radiographic evidence of VZV pneumonitis, but only about one-third of those with abnormal chest radiographs will have respiratory symptoms. With the advent of antiviral treatment and intensive supportive care, the mortality rate has been reduced from 30% to less than 10%. [5]

Symptomatic cerebellar ataxia occurs in about 1 in 4000 varicella cases. Ataxia may develop from several days before to 2 weeks after the onset of varicella, although the neurologic symptoms most often occur simultaneously with rash. The cerebellar dysfunction associated with varicella is self-limited. The vast majority of patients recover without apparent sequelae within 1–3 weeks. Encephalitis, the most serious CNS complication of varicella, has an incidence of 1–2 episodes per 10,000 varicella cases, with the highest incidence in adults and infants. Neurologic symptoms (headache, fever, vomiting, and altered sensorium) most often occur about 1 week after the onset of the varicella rash and may be accompanied by seizures in 29%–52% of cases. The mortality for varicella encephalitis is 5%–10%. Long- term sequelae, including seizure disorders, may be present in 10%–20% of survivors.[5] The demyelinating disorders can be effectively managed using methylprednisolone or i.v immunoglobulins.[6]

Three methods are used for the prevention of VZV infection. First, a live attenuated varicella vaccine is recommended for all children > 1 yr of age (up to 12 years of age). Secondly, varicella zoster immunoglobulins (VZIg) can be administered. This should be given within 96-h of the exposure. Lastly, antiviral therapy can be given as prophylaxis to individuals at high risk of developing complications who are ineligible for vaccine or VZIg.

Haemophagocytic lymphohistiocytosis (HLH), is an uncommon, life-threatening hyperinflammatory syndrome caused by severe hypercytokinemia with excessive activation of lymphocytes and macrophages due to a highly stimulated but ineffective immune process. [7] It may be Primary or Secondary (acquired). The overall reported mortality for acquired HLH exceeds 50%. In cases of infection-associated HLH or malignancy-associated HLH, the immediate treatment of the underlying disease is indicated. [8] Patients may be classified into high-risk and low-risk groups, with only the high-risk groups receiving the etoposide (i.e. VP-16) regimens. Patients who are at low-risk may be treated as effectively with only cyclosporine, corticosteroids or IVIG. Recent case reports show promising results with an anti-TNF- approach and plasmapheresis. Supportive care is needed to ensure that the patient with HLH remains stable until a bone marrow donor can be found. This includes transfusions of RBCs, platelets, and fresh frozen plasma, as well as nutritional support in addition to the treatment protocol. [9]

CONCLUSION:

- Varicella Zoster infection is most often a relatively benign and self-limiting childhood illness. However, the disease can be associated with a variety of serious and fatal complications in both immunocompromised and immunocompetent adults.
- Multi organ dysfunction syndrome is a potentially lethal complication of varicella Infection in adults associated with high morbidity. So, early treatment of varicella in adults along with appropriate supportive measures for suspected complications is required in high risk individuals.
- Haemophagocytic lymphohistiocytosis syndrome can occur very rarely secondary to varicella infection and warning signs must not be overlooked.
- Varicella vaccine should be considered for seronegative immunocompetent individuals and VZIg for post-exposure high risk patients.

REFERENCES:

1. Sudheer P.S. Ahamed, Abdullah Balkhair, Rajan Krishnan. Fulminant Varicella Zoster Infection with Multiorgan Involvement. Nov 2008. Sultan Qaboos Univ Med J. 8 (3): 339 – 343
2. D.H. Dockrel, S. Sundar, B.J. Angus, R.P. Hobson. Chicken Pox (Varicella). Davidson's Principles and Practice of Medicine, 22nd Edition, Elsevier. 2014. Pp 316 – 318
3. Cindy Weinbaum. Varicella – Complications. Centre for Disease Control, Last reviewed – Nov 2016. From www.cdc.gov
4. Whitley R.J, Varicella Zoster Virus Infections. Harrison's Principles of Internal Medicine, 16th ed., New York, McGraw Hill. 2006. Pp 1042 – 1045
5. John W. Gnann, Jr. Varicella – Zoster virus: Atypical Presentations and Unusual Complications. The Journal of Infectious Diseases. 2002. 186 (1): 91-8
6. A.S. Girija, M. Rafeeque, K.P Abdurehman. Neurological Complications of Chicken Pox. Official Journal of Indian Academy of Neurology. 2007. 10 (4): 240-246
7. Anjali Rajadhyaksha, Archana Sonawale, Ajay Agrawal, Kiran Ahire, Juhi Kawale. A Case Report of Haemophagocytic Lymphohistiocytosis (HLH). Journal of the Association of Physicians of India. July 2014. Vol 62: 637 – 41
8. Flavia G. N. Rosado, Annette S. Kim. Haemophagocytic Lymphohistiocytosis – An Update on Diagnosis and Pathogenesis. Am J Clin Pathol. 2013. 139: 713-727
9. Rajani Dube, Subhranshu Sekhar Kar, Samarendra Mahapatro, Rajib Ray. Infection Associated Haemophagocytic Lymphohistiocytosis : A Case Report. Indian Journal of Clinical Practice. July 2013. Vol 24 (2): 163-165