RESEARCH COMMUNICATION

Varicella Outbreak in a Pediatric Oncology Ward: the Manado Experience

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Abstract

<u>Background</u>: Varicella is highly contagious and dangerous disease especially in immunocompromised patients. Children with cancer are at increased risk of severe illness and fatal cases occur. <u>Objective</u>: To describe an outbreak of varicella among in-patient cancer children, family members and staff. Estella Children Cancer Center in Manado, Indonesia with 14 beds and a 15 bed capacity guest house for family members. <u>Methods</u>: A retrospective study of patients, family members and staff who were diagnosed with varicella based on clinical appearance was performed. Follow up was until 28 days from the last patient diagnosis' date. <u>Results</u>: From late February to early May 2009, varicella was affecting 4 among 8 children with leukemia, 1 family member and 1 housekeeping staff. Measurers taken after the index case were oral acyclovir both for patients and contacts, patient isolation, ward disinfection and some chemotherapy interruption. Nevertheless, a second and third wave of varicella occurred. The index case died due to encephalitis. Other patients were non-severe and cured, but one child was lost to follow up. <u>Conclusions</u>: This outbreak highlights the importance of proper prevention and prompt management of varicella in immunocompromised patients. Simple and locally applicable guidelines are needed.

Keywords: Varicella outbreak - pediatric oncology

Introduction

Varicella-zoster virus (VZV) infection is a highly contagious but usually benign and self-limiting disease in otherwise healthy children. On the other hand, immunocompromised children are at great risk of suffering from severe, prolonged, and complicated varicella. It can result in disseminated disease, pneumonia, hepatitis, encephalitis and death (Albrecht, 2009). Before the introduction of effective antiviral therapy, the mortality rate of varicella in cancer children receiving chemotherapy was around 7% in a Western country (Feldman et al., 1975). Severe complications were more likely to develop in patients with acute leukemia than in those with other malignancies (Feldman and Lot, 1987).

Nosocomial transmission of varicella is an ever more serious problem. The increasing number of childhood cancer patients receiving chemotherapy suggests that a greater number of children will be at risk for varicella. Although reports of varicella outbreaks in hospital are rare, some of them were in a pediatric oncology unit (Kavaliotis et al., 1998; Adler et al., 2008).

Several recommendations have been made by the American Academy of Pediatrics (AAP) to prevent the transmission of varicella in healthcare settings, including treatment and isolation of hospitalized infected patients and management of susceptible contacts (AAP, 2009). However, implementation of such recommendations in limited resources setting needs adjustments (Jain et al., 2000).

We describe an outbreak of varicella among hospitalized acute leukemia children, family members and hospital staff. The management of this outbreak was evaluated in regard to limited resources.

Materials and Methods

Clinical setting

Estella Children Cancer Center is a freestanding clinic on the grounds of RD Kandou academic hospital. It is located in Manado, Indonesia and has a capacity of 14 beds. It consists of two third-class wards with four beds each, a second-class ward with 3 beds, a first-class ward with 2 beds and isolation room with 1 bed. Most patients are poor and can not afford treatment by themselves but they get support from the Indonesian Government Welfare Program (GAKIN) and/or the Dutch Estella Fund. Estella center is equipped with a separated guesthouse where

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family members can reside during treatment. It comprises 4 sleeping rooms with a total of 15 beds, sharing kitchen and toilet.

Design

A retrospective study of patients, family members and hospital staff who were diagnosed as varicella was performed. The study period was from the fourth week of February 2009 when the index case was diagnosed, to the first week of May 2009, i.e. 28 days from the last patient diagnosis' date. Diagnosis of varicella was based on clinical appearance, namely an acute generalized maculopapulovesicular rash, without other apparent cause. Patient's parent gave informed consent. Ethics Committee of RD Kandou General Hospital Manado approved this study.

Results

Over a period of around 10 weeks between the last week of February 2009 to the first week of May 2009, 4 cases of varicella were diagnosed among 8 children with acute leukemia (7 acute lymphoblastic leukemia [ALL] and 1 acute myeloblastic leukemia [AML]), 1 case of family member and 1 case of housekeeping staff. All varicella patients with acute leukemia were those with ALL. Table 1 showed the characteristics of ALL children who suffered from varicella. The children with ALL were treated according to the Indonesia-2006 protocol, which is based upon dexamethasone in induction and reinduction (for high risk patients only), and in pulses of 2 weeks every 8 weeks during maintenance.

The index case was a hospitalized 10 year-old girl with T-lineage ALL in induction phase (case patient 1, Figure 1). She had a rash for approximately 2 days before the appearance of more papules on her limbs and face were brought to the attention of doctors and a diagnosis of varicella was made. She was moved to an isolation room of the tropical/infectious disease ward in a distance of 10 meters from Estella-cancer ward. She was treated with oral acyclovir. Her intrathecal methotrexate (IT MTX),
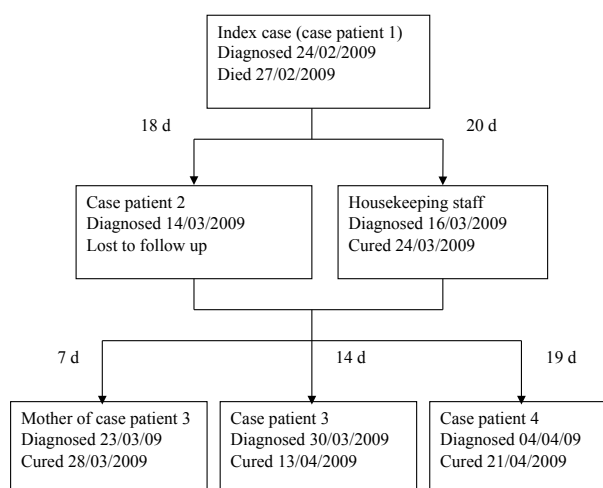
Figure 1. Flow Diagram of Patients Involved in the Outbreak of Varicella

intravenous doxorubicine and L-asparaginase were withheld, but her steroid was continued. She developed seizures and unconsciousness 2 days after having skin lesions. She was diagnosed with encephalitis and died 1 day later. No known source of infection was recognized.

Eighteen days after the index case, 1 child and 1 housekeeping staff had varicella diagnosed. The second case was a 4½-year-old girl with precursor-B ALL in induction phase of treatment (case patient 2). She was given oral acyclovir, continued the steroid and discharged from hospital on the next day by her parent request. She never came back to continue her treatment and is lost to follow up. The housekeeper was treated with oral acyclovir in her home until recovery.

A mother of case patient 3 was diagnosed 7 days after the second wave. Her daughter (case patient 3), 3½ years, presented with papulovesicular lesions on her face, head and back 14 days after the second wave. She was in maintenance phase during dexamethasone block. The last case patient was a 6 year-old girl with precursor-B ALL in maintenance phase on 6-mercaptopurine and methotrexate without dexamethasone block. She presented with lesions

Table 1. Characteristics of Varicella in Children with Acute Leukemia

Case Patient	Leukemia	Phase of treatment	Varicella manifestation	WBC/μL	Lymphocyte count/μl	AST (U/L)	ALT (U/L)	Chemotherapy withheld/continued	Outcome
1	T-lineage ALL, HR	Induction week 4	Lesions on face, trunk, limbs. Encephalitis	3200	1088	189	63	Withheld IT MTX, Continued Dexamethasone	Died
2	Precursor-B ALL, SR	Induction week 3	Lesions on head, back	2300	1357	95	289	Withheld doxorubicine iv, Continued Dexamethasone	Lost to follow up
3	Precursor-B ALL, SR	Maintenance, week27	Lesions on face, head, back	900	702	145	65	Withheld dexamethasone block	Cured
4	Precursor-B ALL, HR	Maintenance, week 19	Lesions on head, neck	3300	1188	34	31	Continued 6-MP & Methotrexate	Cured

WBC: white blood cell, AST: aspartate amino transferase, ALT: alanine amino transferase

on head and neck (case patient 4). Both patients received oral acyclovir and were placed in isolation. The mother of case patient 3 was treated with oral acyclovir and stayed in her home. The flow diagram of patients involved in the outbreak of varicella is presented in Figure 1.

Four other inpatient children who were exposed to the varicella cases were managed with oral acyclovir as well. Two children with ALL and one child with AML were discharged. Another child with relapsed ALL in induction phase was moved to other non-infectious general pediatric ward to continue her treatment. At day 20 from the diagnosis date of index case, the whole cancer ward was cleaned and disinfected.

There was no history of previous varicella infection and/or vaccination in the case patients, family members and housekeeping staff, as well as the non-infected acute leukemia patients. At the time of outbreak, 4 family members stayed in the guest house and were in contact with varicella. These otherwise healthy contacts were advised to avoid exposure as much as possible and to do the general precaution properly (hand-washing, face mask, etc). There was no policy to ask specifically about varicella or vaccination history.

Discussion

This was the first varicella outbreak that occurred in our center from its opening in 2006. Strict isolation was not properly implemented in our case. Although the index case was isolated in a separate building and the following cases were put in isolation room in Estella ward, the family members still met each other in the guesthouse and the patients themselves might go around in the corridor. At the moment of isolation, the index case had had a rash for several days, so she was infectious probably already about a week. The second wave could probably not have been prevented. However, notwithstanding the taken measures, including closing the ward for disinfection, isolating the cases, still a third wave of varicella occurred. Indeed, nosocomial outbreaks of varicella continue to occur even in modern hospitals. The nosocomial spread of varicella is by direct exposure; by contact fomites, as well as by airborne transmission of the virus [Kavaliotis, et al., 1998]. Modern hospitals are frequently constructed with central, re-circulating ventilation systems. This might promote airborne spread of microorganisms. Gustafson et al. (1982) reported an outbreak of airborne nosocomial varicella. Although strict isolation was applied to the index case, an outbreak of varicella did occur in the ward. In their case, the pressure in isolation room was more positive to that of in the corridor. It was suggested that patients hospitalized with varicella be placed in negative-pressure isolation room. A similar finding was reported by Sawyer et al. (1994). VZV DNA was detected in 82% of air samples from rooms housing patients with active varicella, in a distance of 1.2-5.5 meters from patients' bed and for 1-6 days following onset of rash.

Recently, Adler et al. (2008) reported a comparable outbreak. A varicella outbreak occurred in a pediatric oncology unit with outpatient clinics, and affiliated group housing and schoolroom spaces. The housing facility and schoolrooms were places where immunocompromised children, parents, and healthy siblings from multiple families shared common fomites, providing abundant chance for varicella transmission. Additionally, the residents of the housing facility often visited daily the inpatient and outpatient hospital clinic, which resulted in exposure to the case patient. In response to the outbreak, policy at the residential facility was changed. All staff and visitors were asked regarding history of varicella or its vaccination. Information and education materials on varicella were provided. Active surveillance for signs and symptoms of varicella, relocation of families without a history of varicella or its vaccination, and prophylaxis for the immunocompromised patients living at the house were performed.

Prolonged skin lesions were present in two of our cases, except for the index case who died early. The elevation of liver transaminases was not accompanied with other sign or symptom of hepatitis. None of our patients had a lymphocyte count less than $500/\mu1$. Feldman and Lott (1987) reported that more severe VZV infections happened in immunocompromised patients, especially in those with impaired cell-mediated immunity. Lymphopenia (absolute lymphocyte count $<500/ \mu l$) was significantly associated with VZV pneumonia and higher fatality rate. These patients are more likely to suffer from disseminated disease with extensive skin lesions, pneumonia, encephalitis, hepatitis, or other visceral involvement. The most common varicella-related mortality was secondary bacterial infections especially pneumonia (Nguyen et al., 2005).

All varicella cases in this study received oral acyclovir instead of the standard intravenous (iv) acyclovir. Oral acyclovir is much cheaper than the iv one and available in the government essential drug list. All came from either poor families or civil servant familes that had healthcare subsidy or insurance from the government. Few reports supported the effectiveness of oral acyclovir in immunocompromised but uncomplicated varicella children (Meszner et al., 1993; Jain et al., 2000).

Due to the skin lesions, IT-MTX was withheld in our index case. Steroid was continued in index case and in case patient 2 since they were in induction phase. On the other hand, steroid was cancelled in case patient 3 in maintenance phase. There is evidence that prednisone therapy during the incubation period of VZV (10-21 days) increases significantly the risk for developing severe varicella infection. It is possible that dexamethasone is even more dangerous in this respect. Patients who are on ALL treatment and are exposed to varicella should have steroid therapy deferred until after the incubation period. The exception of this approach may be children who are exposed during the ALL remission induction phase. It is probably safe to continue antimetabolite therapy such as 6-mercaptopurine and methotrexate, and vincristine during a VZV incubation period (Hill et al., 2005).

In our setting, all patients who were exposed to varicella but non-affected were given prophylactic oral acyclovir. No prophylaxis was provided to healthy contacts. Both intravenous immunoglobulin (IVIG) and varicella vaccine are expensive and varicella-zoster

immunoglobulin (VZIG) is not available in Manado.

There are 2 principal means of post-exposure prophylaxis in immunosuppressed children i.e. intramuscular VZIG and oral acyclovir or valacyclovir (Weinstock et al., 2004; Skinner et al., 2008. The majority of published literature regarding post-exposure prophylaxis of VZV relates to VZIG. The use of antiviral agents is not supported by randomized trials, but uncontrolled experience suggests that it might be a reasonable option if VZIG is not available (Boeckh, 2006(. In UK, post-exposure prophylaxis is not currently recommended for patients with prior evidence of seropositive VZV antibody, except after hematopoietic stem cell transplantation. Prophylaxis is given only to patients without serum varicella-zoster immunoglobulin G antibody (VZIgG) at diagnosis of their malignancy. However, this was questioned due to the occurrence of varicella in a number of immunocompromised children who all showed VZIgG positivity at diagnosis of their malignancy (Manley et al., 2008). Post-exposure varicella vaccination may be offered to child and adult household contacts without evidence of immunity of immunocompromised persons. It is recommended to vaccinate within 3-5 days from exposure to varicella (CDC, 2007).

Varicella vaccination has not yet been recommended as universal immunization in Indonesia and is not provided routinely for cancer survivor children. Buda et al. (1996) found that varicella exposure and infection were common in children receiving maintenance therapy for ALL. Analysis of 472 children during maintenance period showed 120 exposures to varicella (10/100 patient-years) and 60 cases of varicella (4.6/100 patient-years). Varicella vaccination has been recommended for selected children with ALL in remission. During maintenance phase, the vaccine can be administered after at least 1 year in remission, lymphocyte count >700/μl, and platelet count >100,000/μl. Chemotherapy should be suspended 1 week before until 1 week after vaccination (Sartori, 2004; AAP, 2009). Experience in VUmc Amsterdam with varicella vaccination given in induction for ALL was negative. Several patients developed severe vaccine-related varicella, so we stopped. Fortunately, in VUmc we saw no lethal consequences. Schrauder et al. (2007) reported a fatal experience. They suggested postponing varicella vaccination until at least 9 months after the end of chemotherapy (including maintenance therapy) and not before lymphocyte count of at least 1500/μl. This of course does not help patients during chemotherapy when they are most endangered.

In conclusion, this outbreak highlights the importance of proper prevention and prompt management of varicella in immunocompromised patients. We believe that in limited resources settings, oral acyclovir administration seems quite satisfactory in managing varicella exposures in immunocompromised children. Simple and locally applicable guidelines are needed.

Acknowledgement

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