Original Article

Risk factors for complicated varicella infection in pediatric oncology patients at a tertiary health care facility in Pakistan

Muhammad Matloob Alam[1], Farah Naz Qamar[1], Zalan Wahid Khan[2], Vikram Kumar[1], Naureen Mushtaq[1], Zehra Fadoo[1]

[1] *Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan*
[2] *Medical Students, Aga Khan University, Karachi, Pakistan*

Abstract

Introduction: Varicella zoster infection(VZI) is well recognized as a potential cause of morbidity and mortality in immunocompromised pediatric oncology patients (POP). The purpose of this study was to describe the clinical profile and risk factors for complications and outcomes of VZI in POP treated with acyclovir.

Methodology: Medical records of all POP with a discharge diagnosis of VZI over a period of seven years (2005-2011) were reviewed. The demographic features, underlying malignancy, risk factors for VZI, complications, and outcomes were recorded.

Results: Thirty-six POP with VZI were identified. Leukemia was the most common underlying malignancy (n = 20, 58.8%), followed by lymphoma (n = 7, 20.6%) and solid organ tumors (n = 7, 20.6%). Most of the cases (41%) were observed in children under five. All patients were treated with acyclovir. Varicella-related complications developed in 10 (29%) patients. The most frequent complication was bloodstream infection (n = 3, 8.8%), followed by pneumonia (n = 2, 5.9%), skin infection (n = 2, 5.9%), hepatitis, renal failure, and encephalitis. Independent risk factors associated with complications were age < five years, weight for age < fifth percentile, delay in seeking care (> seven days after onset of symptoms) and severe neutropenia (ANC < 500/cm). One child died secondary to varicella encephalitis.

Conclusion: Our data suggests that young age, poor health-seeking behavior, severe neutropenia, and being underweight are the major risk factors for the development of varicella-related complications in POP in developing countries. These complications could be favorably modified through active immunization of immunocompetent children.

Key words: varicella; immunocompromised; oncology; acyclovir; complications

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Introduction

Pediatric oncology patients are at risk of serious morbidity from varicella zoster infection (VZI) because of their primary disease as well as its treatment [1-3]. The most frequently described complications of VZI in these patients are interstitial or necrotizing pneumonia, hepatitis with acute liver failure, bacterial super infections, and post-infectious inflammatory sequelae (*e.g.*, cerebellar ataxia, hematological abnormalities, and glomerulonephritis encephalitis) [3-8]. The varicella-related mortality in children receiving chemotherapy was around 7%-10% before the era of antiviral therapy, with 32% having visceral dissemination [5]. Since post-exposure prophylaxis with varicella-zoster immune globulin (VZIG) and treatment with antiviral therapy were implemented, deaths from varicella are now very rare [9]. However, despite the best preventive measures, VZI is a significant clinical problem in pediatric oncology patients, especially in developing countries where the varicella vaccine is not included in the routine immunization schedule [10]. Thus, there are large numbers of susceptible individuals, and the issue is further compounded by the unavailability of VZIG, limiting the therapeutic options in exposed immunocompromised children. There is limited data on morbidity and mortality associated with VZI in pediatric oncology patients from developing countries, especially South Asian countries. We therefore conducted this study to describe the clinical features and to identify the risk factors associated with complicated varicella and treatment outcome of VZI in pediatric oncology patients at a tertiary heath care facility in Pakistan.

Methodology

Study design and setting

A retrospective chart review of all pediatric oncology patients admitted with a diagnosis of VZI to the pediatric oncology unit of Aga Khan University Hospital (AKUH) in Karachi, Pakistan, over a period of seven years, between 2005 and 2011, was performed. AKUH is a 600-bed tertiary health care facility and is accredited by the international arm of the Joint Commission International Accreditation Survey (JCIA). There is a 10-bed pediatric oncology ward along with a five-bed special care unit within the Pediatric Department. A total of 11,465 patients were admitted in the last seven years; the average number of admissions was 1,638 per year. There is a separate day care facility for chemotherapy administration and blood transfusions.

Patient population and definition

Patients between one month and 15 years of age who were admitted to the pediatric oncology ward between 2005 and 2011 with a diagnosis of VZI were included. For the purpose of this study, the attending physician's clinical diagnosis of varicella, based on varicella clinical case definition, set by the United States Centers for Disease Control and Prevention (CDC)/ Council of State and Territorial Epidemiologists (CSTE) Guidelines 2009 [7,11] was accepted, since no viral cultures or serologic tests were done to confirm the diagnosis. Bloodstream infection (BSI) and pneumonia in immunocompromised patients (PNEU3) was defined according to the criteria established by CDC/NHSN guidelines [12].

Data collection

Records were retrieved using a health information management system (international classification of diseases [ICD] 2008; code 0520). The data collected included demographic features, underlying malignancy, phase of chemotherapy, duration of symptoms before admission, treatment received, and length of hospital stay. Varicella-related complications were defined as a condition or event occurring within 14 days of the onset of varicella, and to which the varicella zoster virus infection may have contributed in some measure (*e.g.*, sepsis, pneumonia, skin infection, hepatitis, encephalitis) [5]. Laboratory data such as total leukocyte counts, absolute neutrophil counts (ANC), absolute lymphocytes counts (ALC), platelet counts, and yield of blood culture (if applicable) were retrieved. The final outcome in terms of development of complications or uneventful recovery was identified.

Statistical analysis

The overall incidence of VZI in pediatric oncology patients was determined by dividing the varicella-infected cases by the total number of admissions to the pediatric oncology unit during the study period; the yearly incidence rate was calculated by dividing the varicella-infected cases by the total number of admissions in that year. For analysis, SPSS version 20.0 was used. Frequencies were computed for qualitative variables and median and interquartile range were computed for quantitative variables. The subjects were stratified according to the development of complications. Logistic regression analysis was performed to identify the independent risk factors for development of varicella-related complications. Adjusted odds ratio and confidence intervals are reported.

Ethical approval

The study was granted exemption by the Ethical Review Board (ERB) of Aga Khan University, Karachi (2250-Ped/ERC-12).

Results

A total of 11,465 pediatric patients were admitted to the oncology ward during the study period, of which 36 developed VZI. Two patients had two episodes of varicella infections, and the two secondary cases were excluded. The demographic and clinical data of 34 pediatric oncology patients with VZI were analyzed. The estimated overall incidence rate was 0.3%. Yearly incidence over the seven-year study period varied from 0.17% to 0.6%.

The most common underlying malignancy was acute lymphoblastic leukemia (n = 18, 53%), followed by lymphoma and solid organ tumors (Table 1). The median age at diagnosis of this cohort was 6.0 (interquartile range 4.7-9.3) years. The characteristics of pediatric oncology patients who developed VZI are given in Table 1. The most common presenting symptom was a rash, developed in 78.2% of the patients and frequently accompanied by fever. Other associated symptoms included anorexia, abdominal pain, body malaise, cough, vomiting, and odynophagia. All patients were hospitalized and received intravenous acyclovir for an average of 3.7 days (range 1 to 6 days) before switching to the oral form to complete between 7 and 10 days.

Table 1. Characteristics of pediatric oncology patients who developed varicella (n = 34)

Characteristics		**Number (%)**
Gender	Male	15 (44.1)
Age in years	0-5 years	14 (41.2)
	6-10 years	13 (38.2)
	11-15 years	7 (20.6)
Type of malignancy		
Acute leukemia	Acute lymphoblastic leukemia	18 (52.9)
	Acute myeloid leukemia	2 (5.9)
Lymphoma	Hodgkin's lymphoma	4 (11.8)
	Non-Hodgkin's lymphoma	3 (8.8)
Solid tumors	Rabdomyosarcoma	2 (5.9)
	Brain tumor	2 (5.9)
	Osteocsarcoma	1 (2.9)
	Retinoblastoma	1 (2.9)
	Renal rabdoid tumor	1 (2.9)
Absolute neutrophil count	0-500/cm	6 (17.6)
	501-1000/cm	10 (29.4)
	> 1000/cm	16 (47.0)
Absolute lymphocyte count	0-500/cm	9 (26.5)
	501-1000/cm	12 (35.3)
	> 1000/ cm	13 (38.2)
Interval between last chemotherapy and development of varicella	< 2 weeks	20 (58.8)
	> 2 weeks	14 (41.2)
Onset of symptoms prior to admission	< 7 days	27 (79.4)
	> 7 days	7 (20.6)
Length of stay (days)	Stay < 7 days	19 (55.9)
	Stay > 7 days	15 (44.1)
Outcome	Discharged	33 (97.1)
	Expired	1 (2.9)

Table 2. Varicella-related complications (n = 10)

Complications	**Number (%)**
Bloodstream infection *	3 (8.8)
Pneumonia**	2 (5.9)
Skin infection	2 (5.9)
Hepatitis	1 (2.9)
Encephalitis	1 (2.9)
Renal failure	1 (2.9)

*Isolates: *Streptococcus pneumoniae, Staphylococcus epidermidis, Staphylococcus species.* **One patient with pneumonia also had pleural effusion

Table 3. Risk factors of patients who developed varicella-related complications (n = 34)

Variables	With complications (n = 10)	Without complications (n = 24)	p-value	Crude OR (CI)	Adjusted OR (CI)
Male	7	8	**0.059**	4.7 (0.95-23.04)	--
Age (0-5 years) > 5 years	7 3	7 17	**0.035**	5.7 (1.13-28.45)	**86.9 (1.49-5090.71)**
Primary diagnosis (ALL)	8	10	**0.054**	5.6 (0.97-32.19)	--
Maintenance phase of chemotherapy	4	8	**0.253**	2.4 (0.53-11.11)	--
Received chemotherapy in the preceding 2 weeks	9	11	**0.037**	10.6 (1.16-97.59)	--
Admission after > 7 days of symptoms	5	2	**0.014**	11.0 (1.64-73.97)	**21.2 (1.00-492.66)**
Weight < 5th percentile	9	12	**0.032**	5.0 (0.75-33.49)	**25.6 (1.00-661.16)**
ANC (< 500/cm)	4	2	**0.042**	7.3 (1.07-50.15)	**32.7 (1.12-954.91)**
ALC (< 500/cm)	4	5	**0.256**	2.5 (0.51-12.59)	--
Platelets count (< 50,000/cm)	3	3	**0.235**	3.0 (0.49-18.42)	--
Length of stay (>7days) <7 days	8 2	7 17	**0.034**	6.7 (1.15-38.59)	--

OR: odds ratio; CI: confidence intervals; ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count; ALC: absolute lymphocyte count

A total of 10 patients (29%) developed varicella-related complications. The most frequent complication was bloodstream infection (n = 3, 8.8%), followed by pneumonia (n = 2, 5.9%) and bacterial super infections of skin lesion (n = 2, 5.9%), as shown in Table 2. On regression analysis, age under five years, delay in seeking care (> seven days after the onset of symptoms), severe neutropenia (ANC < 500/cm) on admission, and being underweight (< fifth percentile) were identified as risk factors for the development of varicella-related complications among pediatric oncology patients with VZI (Table 3). The overall recovery rate was 97.1%. One patient who developed varicella encephalitis expired during his stay in the intensive care unit.

Discussion

We report a high rate of varicella-related complications as compared to international data [13,14]. Delay in seeking care seems to be the most likely reason for this high rate. Due to multiple social, cultural, and financial constraints, care seeking is delayed as evidenced by recent data from Pakistan [15]. Lack of recommendation of the varicella vaccine in the national immunization schedule increases the risk of exposure in these high-risk children as evidenced by reports from countries where susceptible children one year of age and older in the general population are routinely vaccinated [13,16,17]. Hence, VZI remains a significant problem for oncology patients in developing countries where access to diagnosis and care is not readily accessible [10]. The incidence of seropositivity for varicella in the healthy population under five years of age was found to be 30%, whereas up to 50% had seroconverted by adolescence in Pakistan, similar to what has been reported from other tropical countries [18,19]. The high percentage of seronegativity in the younger age group predisposes immunocompromised children to infection and increases their risk for exposure.

Patients with an underlying diagnosis of acute lymphoblastic leukemiaand children less than five years of age were observed to develop complications more than any other age group, which was consistent with other studies [5]. This is also explained by the high rate of seronegativity in this group.

Recently, studies have reported a varicella-related complication rate of approximately 20% in VZV-infected, immunocompromised patients treated with antiviral treatment [3,20]. Most subjects in these studies sought care within the first three days of the onset of symptoms. The delay in care seeking probably explains the higher complication rate seen in our study. Before the introduction of antiviral therapy, the mortality rate of VZI in children with cancer was reported to be 7%-10%, with rates reaching up to 55% in cases with visceral involvement [5,21,22]. The majority of our patients recovered from the disease and its complications, with an overall recovery rate of 97%. We report a mortality rate of 3% that is much lower than the rate reported by a previous study (13.6%) of immunocompromised children [23].

Systemic corticosteroid therapy is said to increase morbidity, especially when administered during the

incubation period of varicella infection [24], and is associated with fatal complications despite the administration of VZIG [25]. Children who had received immunosuppressive chemotherapy within two weeks of the development of VZI were at higher risk of complications compared to others. This implies that the more severe the immunosuppression, the greater the risk of developing varicella-related complications, as described in previous studies [9].

Post-exposure prophylaxis with VZIG has been recommended when significant exposure to varicella has occurred [26]. However, cost and unavailability limit this option [27]. All patients in our study were hospitalized for therapeutic antiviral treatment. None of our patients developed adverse effects to acyclovir as reported in other studies [20]. With the exception of one fatal case, antiviral treatment was effective in preventing mortality, though complications occurred [28]. We identified severe neutropenia as an independent risk factor for the development of varicella-related complications in our study cohort. This is in contrast to other reports in the literature, which show a higher risk of complications in lymphopenic children [5]. Varicella pneumonitis is a fatal complication, especially when ANC count is < 300/cm, and it is associated with a 25% mortality rate [9]. However, both of our patients who had pneumonia recovered uneventfully.

Although many authors still do not recommend varicella vaccination for children receiving chemotherapy or radiotherapy because of potentially fatal complications of the vaccination, the risk associated with withholding chemotherapy and the rarity of death from VZI should be considered [4]. However, recommendation of routine varicella vaccination in the general population, especially for household contacts of immunocompromised children and caregivers who have negative history of VZI or shingles, may be the most effective practice to reduce the burden of varicella exposure, disease, and complications in these high-risk children [4,29].

Limitations of this study include its retrospective design; we were not able to assess the exposures and reasons for delay in seeking care and we may have missed patients who were not admitted and opted for outpatient or day care treatment. This was a single-center study; however, we assume that the results are generalizable to all developing countries where VZIG is unavailable for post-exposure prophylaxis and varicella vaccination is not part of the vaccination schedule. The small sample size explains the wide confidence intervals observed on multivariate analysis. While the results of our study are certain, firm recommendations require additional studies.

Conclusions

Varicella-related complications develop in one-third of infected pediatric oncology patients in developing countries. Young age, poor health-seeking behavior, severe neutropenia, and being underweight are the major risk factors for the development of varicella-related complications. Treatment with antiviral therapy prevents complications and reduces mortality. However, national guidelines for varicella vaccination particularly for household contacts of this high-risk group are needed to prevent this infection from occurring.

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Corresponding author

Dr. Muhammad Matloob Alam
Fellow Pediatric Hematology & Oncology
Department of Paediatrics & Child Health
Aga Khan University Hospital
Stadium Road, PO Box 3500
Karachi 74800, Pakistan
Phone (+92-021) 34864795 or 092-3002802859
Fax (+9221) 34934292
Email: dr.matloobalam@hotmail.com or matloob.alam@aku.edu

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