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Panton–Valentine Leukocidin-Positive Methicillin-Resistant *Staphylococcus aureus* Infections in Children With Cancer

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Abstract

Background—New strains of methicillin-resistant *Staphylococcus aureus* (MRSA) which frequently carry the Panton–Valentine leukocidin (PVL) genes have been recognized to cause invasive infections in otherwise healthy children and adults. However, the epidemiology of PVL-positive MRSA infections has not been described in children or adults with cancer.

Procedure—The epidemiology of MRSA infections in patients with cancer was retrospectively studied from 2000 to 2007. Molecular typing was performed by polymerase chain reaction (PCR) for the detection of the PVL genes. *Staphylococcus* cassette chromosome (SCC) *mec* and *spa* typing was performed on all PVL-positive isolates.

Results—A total of 88 MRSA isolates from clinically distinct infectious episodes were collected from 88 patients with cancer during the 8-year study period. Infections were predominant in the skin and soft tissues (SSTI; $P = 0.0003$). PVL-positive isolates, bearing the type IV SCC_{*mec*} element, encoding the gene for methicillin resistance, increased significantly during this period ($P = 0.043$) and comprised 35 of 88 (40%) MRSA isolates. Of these 35 isolates, 32 belonged to *spa* type 8 and were USA300 genotype. Patients infected with PVL-positive strains did not have more SSTI ($P = 0.166$) or bacteremia ($P = 0.510$) as compared to patients with PVL-negative strains. A greater percentage of PVL-positive isolates were susceptible to ciprofloxacin ($P = 0.006$).

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Conclusions—PVL-positive MRSA infections are not associated with a higher morbidity as compared to PVL-negative MRSA infections in children with cancer.

Keywords

cancer; children; methicillin-resistant *Staphylococcus aureus*; Panton-Valentine leukocidin

INTRODUCTION

Staphylococcus aureus is among the more prevalent pathogens isolated from hospitalized patients. *S. aureus* causes a wide range of syndromes, from minor skin and soft tissue infection (SSTI) to life-threatening sepsis and toxic shock syndrome. An increase in the incidence of methicillin-resistant *S. aureus* (MRSA) infections was noted worldwide in the late 1990s [1–4]. This increase was accompanied by the isolation of MRSA isolates from community-acquired infections among previously healthy individuals with few or no traditional healthcare-associated risk factors [2]. Suppurative skin infections and necrotizing pneumonias are some of the well-known associations with these new strains [5]. Molecular typing of such isolates has shown that they are largely caused by MRSA strains which carry the Panton–Valentine leukocidin (PVL) genes [5] and belong to USA300 [6], multilocus sequence type 8 (ST8), the most common strain causing community-acquired MRSA (CA-MRSA) infections in the US. Further, they typically carry the type IV staphylococcus cassette chromosome (SCC) *mec* element [7], encoding the gene for methicillin resistance; and are typically susceptible to clindamycin [8]. Panton and Valentine first associated the leukotoxin with SSTI in 1932 [9]. However, PVL may not be the factor responsible for the greater virulence of CA-MRSA but may be a marker for CA-MRSA and other virulence genes associated with it [10].

The clinical course of PVL-positive *S. aureus* infections tend to be more severe than PVL-negative infections [5]. Increasing numbers of children and adults with invasive infections such as necrotizing fasciitis [11], musculoskeletal infections [12], and bacteremia [13] caused by these strains, both in the outpatient as well as in the hospital setting [14], have been reported.

The role of these new MRSA strains in causing infections in children and adults with cancer is presently unknown. It is hypothesized that PVL-positive CA-MRSA strains cause more morbidity than PVL-negative strains in this population.

PATIENTS AND METHODS

This retrospective cohort study included all patients with cancer at St. Jude Children's Research Hospital (SJCRH), who were diagnosed with PVL-positive and PVL-negative MRSA infection over an 8-year period from January 2000 to December 2007. The study was approved by the Institutional Review Board at SJCRH. Patients with MRSA infection were identified through a review of clinical microbiology culture results.

SJCRH is a tertiary care children's research hospital which treats approximately 3,000 patients with cancer each year referred immediately after diagnosis of their underlying malignancy, from across the US, but mostly from within a 600 mile radius of Memphis. The typical duration of follow-up is for 10 years after diagnosis, or until 18 years of age, whichever is later.

Epidemiological Analysis

The number of cancer patients with MRSA infections at SJCRH between January 2000 and December 2007 was determined. Data abstracted from medical record review included the following independent variables: patient age, gender, race; underlying malignancy, remission, and transplant status; fever at presentation, duration of infection-related symptoms, and complications; absolute neutrophil count at diagnosis of infection; site of infection; co-pathogens; antibiotic therapy; inpatient or outpatient status at time of infection, and admission to an intensive care unit.

Specimen sources from which MRSA isolates originated were classified into four main groups: sterile sites including blood and cerebrospinal fluid (CSF); SSTI including pustules and abscesses; respiratory sites including tracheal aspirates and bronchoalveolar lavage specimens; and other clinical sites such as body fluids, bone, eye, and ear infections.

Microbiologic Analysis by Phenotypic Methods

Isolates were initially identified as *S. aureus* by Staphaurex plus® (Remel Europe Ltd, Dartford, Kent, UK). Bacterial isolates were subsequently preserved at -80°C, prior to retrieval, with only the first isolate for each infectious episode, from each patient during the study period, included in the analysis. Recurrent infections were defined for the purpose of epidemiological analysis as positive isolates obtained from the same case, 30 days or more after the last positive culture. Only the first infection was included in the analysis.

Antimicrobial susceptibility testing was previously performed on all isolates. Screening for methicillin resistance was performed using disk diffusion using a 1-µg oxacillin disc and by growth on Mueller–Hinton agar containing 4% NaCl and oxacillin (6 µg/ml), after an incubation period of 24 hr at 35°C. The Clinical and Laboratory Standards Institute (CLSI) methodology was followed in all testing methods [14]. As most of the isolates had been initially evaluated prior to the implementation of cefoxitin disk testing, all were re-screened for methicillin resistance using 30 µg cefoxitin disks (BD BB1 Sensi-Disc, Becton Dickinson and Company, Sparks, MD). A zone <23 mm was interpreted as confirming methicillin resistance. Mupirocin resistance was confirmed by using a 5 µg mupirocin disk (kindly provided by GlaxoSmithKline, Collegeville, PA). Isolates that had a zone diameter of <13 mm were considered resistant to mupirocin. Other antibiotics tested included penicillin, vancomycin, clindamycin, trimethoprim–sulfamethoxazole (TMP–SMZ), erythromycin, gentamicin, and ciprofloxacin. The latter testing was performed by Vitek® analysis (Vitek 32 system, BioMerieux, Inc., Durham, NC). Results were determined after 24 hr of incubation at 35°C according to CLSI breakpoints. For all isolates that were erythromycin-resistant and clindamycin-susceptible, detection of the inducible macrolide–lincosamide–streptogramin B resistance phenotype was performed by disk diffusion with clindamycin and erythromycin disks set 15–20 mm apart (D test) [15]. Results of clindamycin resistance included the inducible resistance phenotype.

Molecular Typing of *S. aureus* Isolates

Frozen crude lysates of pelleted, liquid cultures were assayed by polymerase chain reaction (PCR)-based genotyping. PCR amplifications were performed using a multiplex PCR protocol previously described by Perez-Roth et al. [16] for the simultaneous detection of *nuc* gene (encoding the thermostable nuclease of *S. aureus*) and *mec A* gene (encoding the gene for methicillin resistance). The presence of the *lukF* and *lukS* genes of PVL was determined by PCR as previously described [17]. Detection of Toxic Shock Syndrome Toxin (TSST-1) was by PCR as described by Lovseth et al. [18] *SCCmec* typing and *spa* typing was performed on isolates which expressed the PVL genes. The *SCCmec* types were determined by PCR typing of the *mec* and the *ccr* gene complex as described previously by Okuma et al.

[19] DNA sequence-based typing of *S. aureus* protein A (*spa*) gene was performed as previously described using template DNA extracted from overnight cultures [20,21]. The USA pulse field types were inferred from the *spa* types by using the Based Upon Repeat Pattern (BURP) algorithm to cluster the *spa* types into related families or *spa* Clonal Clusters (*spaCC*). The Ridom StaphType software tool and our pulsed-field gel electrophoresis (PFGE) determinations were used to correlate the PFGE type to the *spaCC* [22].

Statistical Analysis

Descriptive statistics, including frequencies and percentages, were obtained for the demographic and treatment variables of the patients with cancer and MRSA infection. The trend of PVL-positive MRSA infection was evaluated by exact logistic regression with year as the independent variable. The associations between PVL-positive MRSA infection and the independent variables were individually evaluated by univariate exact logistic regression to counterbalance the small cell counts. Those variables that emerged as marginally significant (P -value <0.10) in the univariate analysis were included in the multiple exact logistic regression model. The appropriateness of the models was evaluated by the Hosmer and Lemeshow [23] goodness-of-fit tests. Exact chi-square test was applied to compare infection site between PVL-positive and PVL-negative infections and age and race between patients with MRSA infection and cancer and all patients with cancer. One-sample one-side binomial test was applied to test the majority of SSTI among MRSA infections. All analyses were performed in statistical software package SAS 9.1.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Clinical Epidemiology of MRSA Infections

A total of 88 MRSA isolates from clinically distinct infectious episodes were collected from 88 patients with cancer during the 8-year study period. The mean age of children with MRSA infection was 8 years (range: 9 months to 24 years). Sixty-five patients (74%) were children from 0 to 12 years of age, 11 (12%) were adolescents from 12 to 18 years of age, and 12 (14%) were 18–24 years of age. Forty-seven (53%) of infected patients were males. Forty-two (48%) were African-Americans and 42 (48%) were White (Table I). There was a higher proportion of children 0–12 years of age with MRSA infection and cancer (0.60%), as compared to patients 18–24 years of age with MRSA infection and cancer (0.16%; $P < 0.0001$, P -value based on the exact chi-square test; Table II). There was a higher percentage of African-Americans among patients with MRSA infection and cancer (0.91%), as compared to Caucasians and other patients with MRSA infection and cancer (0.22%; $P < 0.0001$, P -value based on the exact chi-square test; Table II). Whites contributed to 19,877 out of 25,455 (78%) patients with cancer.

The distribution among patients diagnosed with leukemia/ lymphoma, solid tumor, and brain tumor was 33.0%, 38.7%, and 28.3%, respectively. More than half the patients (59%) were in remission and 52% were inpatients.

Infections included pustules (14 patients) and abscesses (46 patients) in the skin and soft tissue of the gluteal region and the extremities (60 of 88 patients (68%); $P = 0.0003$). The abscesses varied in size from 2–5 cm. Other sources included blood stream (10), respiratory tract (11), and other sites (7).

Only 27 patients (31%) had fever and 9 patients (10%) had complications attributable to the MRSA infection, which included port abscesses in three patients, hypotension in two patients, pneumonia in one patient, embolic skin lesion in one patient, and adult respiratory distress syndrome in two patients (Table I).

MRSA infection re-occurred in 10 patients, 7 of which were cutaneous infections. All recurrences were seen one or more years after complete resolution of the initial infection, and occurred at sites other than that of the initial infection. No patient had more than one recurrent infection. There were no patients who suffered a relapse of infection within 30 days after discontinuation of antibiotic therapy.

Epidemiology of MRSA Infections Associated With PVL-Positive Strains

There were 35 patients with PVL-positive MRSA infection out of a total of 88 patients with MRSA infection (40%). The logistic fit gave a P -value 0.043 (odds ratio 1.29; CI: 1.01–1.65; Fig. 1), suggesting an increasing trend over time. All the PVL-positive isolates carried the type IV SCC *mec* element. Of these 35 isolates, 32 belonged to *spa* type 8 and were USA300 genotype. Two isolates were *spa* type 12 and one was non-typeable. Two of the 88 MRSA isolates expressed the TSST-1 gene and were PVL negative.

Patients with PVL-positive MRSA did not have significantly more skin infections ($P=0.166$) or bacteremia ($P=0.510$) as compared to patients with PVL-negative MRSA infections. The mean ANC of all patients with MRSA infection was 4,072 cells/ μ l. There was no statistical difference in the number of patients with PVL-positive and PVL-negative MRSA infections with an ANC <500 cells/ μ l ($P=0.65$). None of the other variables including age, gender, race, presence or absence of fever, inpatient or outpatient status, complications, or remission status were significantly different between the PVL-positive and PVL-negative groups.

Of the 88 patients, 65 were receiving prophylaxis with TMP-SMZ for *Pneumocystis jirovecii* infection. This prophylactic treatment did not predispose patients to PVL-positive or PVL-negative infections ($P=0.124$) or to the presence or absence of fever (0.579) and complications ($P=0.301$).

Antimicrobial Susceptibility Patterns

Resistance of the MRSA isolates to ciprofloxacin, clindamycin, erythromycin, and gentamicin was 23%, 18%, 81%, and 5%, respectively. Two isolates (2%) demonstrated low-level resistance to mupirocin. With the test performed we were unable to determine if these two isolates had high-level resistance to mupirocin. All the isolates were susceptible to TMP-SMZ and vancomycin.

Only 6% of the PVL-positive isolates were resistant to ciprofloxacin as compared to 34% of PVL-negative MRSA isolates ($P=0.006$; P -value based on exact multiple logistic regression model). The differences in resistance to clindamycin, erythromycin, gentamicin, TMP-SMZ, vancomycin, and mupirocin were not statistically significant between the two groups.

DISCUSSION

The data presented here discuss the epidemiology of PVL-positive and PVL-negative MRSA infections in children with cancer. A significantly greater number of patients with MRSA infection were of African-American ancestry as compared to all patients with cancer. This association between MRSA infection and African-American race has been reported in other studies [24]. The reason for the relative overrepresentation of African-Americans is not known. The relative predominance of MRSA infection in younger children with cancer is a novel finding and needs to be confirmed. Patients with PVL-positive MRSA infections did not have more skin infections, bacteremia, or other complications as compared to patients with PVL-negative MRSA infections.

Resistance to clindamycin was seen in 6% of our PVL-positive isolates. A 100% incidence of resistance to clindamycin has been reported in a group of 30 adult men, in an HIV clinic, infected by a multidrug-resistant USA300 clone [25]. Increasing resistance to clindamycin in high-risk populations may contribute to the emergence of recurrent or persistent CA-MRSA infections.

S. aureus bacteremia in children with cancer was last studied retrospectively in 1978 by Ladisch et al. who reviewed 70 episodes of bacteremia over a 9-year period. Serious complications included only three cases of pneumonia and one of myositis [26]. The majority (60%) of the septic episodes occurred when the patient's primary disease was in relapse; granulocytopenia with an ANC <500 cells/μl preceded 77% of the episodes. Blood cultures taken after the institution of antibiotic therapy were uniformly negative. There were only three deaths, all due to pneumonia, and no focal complications of endocarditis or osteomyelitis were observed. The low incidence of complications is in contrast to the clinical syndrome with Gram-negative bacterial sepsis. Findings in the present series differed in that the majority (59%) of the patients were in remission and only 20% had an ANC <500 cells/μl. Fever was seen in only 31% of patients and only 10% had complications. Only 10 patients (11%) had bacteremia, 7 of them catheter-related.

The low morbidity with *S. aureus* infections in patients with cancer, even with the advent of these new virulent strains which can cause serious infections in otherwise healthy young people, needs to be confirmed. Patients who received prophylaxis for *P. jirovecii* with TMP-SMZ did not have a lower incidence of fever or complications, indicating that the administration of prophylactic antibiotics did not account for mild courses. Another possible explanation may be early institution of empiric antibiotic therapy for fever; however, two-third of the patients did not have fever and may have presented with a later stage of infection. Immune suppression and dismodulation may also be partially responsible for the clinical picture seen in these patients.

PVL is a bicomponent, pore-forming leukotoxin initially designated "substance leukocidine" by Van de Velds in 1894 because of its ability to lyse leukocytes. In vitro, it has been shown to induce apoptosis of neutrophils in vitro, by targeting the mitochondrial pathway [27]. The depletion of neutrophils could enhance the pathogenicity of *S. aureus*. Neutropenia is significantly more frequent in patients with necrotizing pneumonia caused by PVL-positive *S. aureus* than in patients with PVL-negative *S. aureus* [28]. While a role for PVL in dermonecrosis in rabbits has been established [29], evidence to show that PVL is a virulence determinant in mouse models of staphylococcal skin infections and pneumonia has been inconsistent [30,31].

PVL-positive MRSA strains may have been introduced into the hospital by the patients who require admission for management of their infections. Klevens et al. [32] reported a 16–22% incidence of invasive healthcare-associated infections caused by USA300. Popovich et al. [33] reported that the proportion of blood stream infections caused by community genotype MRSA increased from 24% to 49% during 2000–2006.

Our study had several limitations including its retrospective nature and small sample size. Exact multiple logistic regression was used since it tends to be more conservative in detecting smaller effect sizes and allows adjustment for comparisons [34]. The test did not account for potential confounders. Although this study analyzes a very large cohort of patients over an 8-year period, owing to the sample size the statistical test may have had limited power to detect some associations. Further studies are required to test the validity of these observations in children and adults with cancer.

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Fig. 1. Increasing proportion of patients with cancer and Panton–Valentine leukocidin (PVL)-positive MRSA infections between 2000 and 2007 ($P=0.043$).

TABLE I**Epidemiology of MRSA Infections in 88 Patients With Cancer**

Characteristic	No.	%
Mean age	8 years	
Males	47	53
Race		
White	42	48
AA	42	48
Others	4	4
Patients in remission	52	59
Inpatients	46	52
Fever (temp. >38.3°C)	27	31
Complications	9	10
SSTI	60	68
Bacteremia	10	11
Absolute neutrophil count <500 cells/ μ l	18	20

AA, African-American; MRSA, methicillin-resistant *Staphylococcus aureus*. Data are number (%) of patients, unless otherwise indicated.

TABLE II

Comparison of the Demographic Data of Cancer Patients Without MRSA Infections to Cancer Patients With MRSA Infections

Characteristic	Cancer patients without MRSA (n =25,455)	Cancer patients with MRSA (n =88)	MRSA proportion (%)	P-value
Age: 0–12 years	10,802	65	0.60	<0.0001
12–24 years	14,653	23	0.16	
Male	13,860	47	0.34	0.915
Female	11,595	41	0.35	
AA	4,591	42	0.91	<0.0001
White and others	20,864	46	0.22	

AA, African-American; MRSA, methicillin-resistant *Staphylococcus aureus*. Data are number (%) of patients, unless otherwise indicated.