Clinical Case Reports and Reviews

Case Report ISSN: 2059-0393

Systemic lupus erythematosus and hepatitis C are risk factors for cellulitis in patients with invasive pneumococcal disease

Thomas J. Marrie[1]* and Gregory J. Tyrrell[2]

[1]Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, USA

[2]The Provincial Laboratory for Public Health (Microbiology) and the Division of Diagnostic and Applied Microbiology, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, USA

Abstract

Background: Cellulitis due to *Streptococcus pneumoniae* is uncommon. A longitudinal study of invasive pneumococcal disease in Alberta, Canada gave us an opportunity to better define this entity.

Methods: From January 2000 to March 2013 we studied all patients with invasive pneumococcal disease (IPD) in Northern Alberta and from 2000 to 2004 patients in Southern Alberta with this infection were also studied.

Results: 68/3243 (2.1%) patients with IPD had cellulitis and in 45% of these the cellulitis was present on admission. Lower extremities and periorbital areas were involved in 61% of patients. Children rarely (7%) had involvement of the lower extremities while 71% of adults had such involvement. Two patients had necrotizing fasciitis. Hepatitis C, odds ratio 2.97; 95% CI (1.67 -5.31) and systemic lupus erythematosus 7.88 (2.79 – 23.35) were risk factors for cellulitis in these patients with IPD. There was no serotype predilection for causing cellulitis and 25%, 32% and 39% of the serotypes were contained in the PCV 7, PCV 13 and PPV 23 vaccine respectively.

Conclusions: Pneumococcal cellulitis is more common than previously thought and hepatitis C and SLE are risk factors.

Introduction

The first case of *Streptococcus pneumoniae* cellulitis was reported in 1917 [1]. Since then there have been sporadic cases reports of this entity with a collection of 45 such cases reported to 2006 summarized by Sabio *et al.* [2]. A previous review of 30 cases by Parada and Maslow suggested that there were two distinct syndromes – cellulitis of the limbs associated with a history of ethanol abuse, injection drugs and diabetes mellitus; patients with systemic lupus, nephrotic syndrome and hematological disorders where face and neck cellulitis predominated [3].

From 2000 to March 2013 we studied all patients with invasive pneumococcal disease (IPD) in Northern Alberta and for the first five years of this time all patients in Alberta with this infection were included. This gave us the opportunity to compare patients with cellulitis with those who did not.

Materials and methods

Definitions

Cases of IPD were defined as per the Canadian national case definition [4]. This required the isolation of *S. pneumoniae* from a normally sterile site such as blood, CSF, pleural fluid, biopsy tissue, joint aspiration, pericardial fluid, or peritoneal fluid. Pneumococcal isolates were submitted to the Provincial Laboratory for Public Health (PPHL) located in Edmonton, Alberta, for serotyping. Only one isolate was counted per case within a 30 day period unless the second isolate was a different serotype.

Cellulitis was defined as an acute, spreading pyogenic inflammation of dermis and subcutaneous tissue. The involved area is warm, tender, erythematous, swollen and lacks sharp demarcation [5]. In general a physician diagnosis of cellulitis was accepted for a case to be counted as cellulitis in our IPD database.

Clinical data collection

Research nurses prospectively collected sociodemographic, clinical, functional, and laboratory data using a standardized case report data collection form previously described. From 2000 to 2004 data were collected on all patients in Alberta with IPD and from 2005 to 2013 only patients in Northern Alberta were studied. The research nurses received training prior to data collection. In addition to the case report form, standard operating procedures document, definitions, drug classification and underlying illness categorization were part of their working documents. With respect to underlying illnesses, if the attending physician recorded such an illness it was accepted as such for the purpose of the study, although renal failure and hepatic failure were

Correspondence to: Thomas J. Marrie, 59 Sprucebank Lane, RR 1 Chester Basin NS; B0J 1K0, Tel: 902 275 4078; E-mail: t.marrie@dal.ca

Key words: *Streptococcus pneumonia, cellulitis, hepatitis C, systemic lupus erythematosus, invasive pneumococcal disease*

Received: June 25, 2016; **Accepted:** July 16, 2016; **Published:** July 19, 2016

specifically defined. Renal failure was defined as an increase in serum creatinine of 100 mM/L over a baseline normal creatinine, requirement for hemodialysis or a baseline creatinine of over 200 mM/L. Hepatic failure was present if indicated by the attending physician.

Identification and serotyping of *S. pneumoniae* isolates

S. pneumoniae isolates received at the PPHL were confirmed as *S. pneumoniae* based on characteristic morphology and optochin susceptibility [6]. All pneumococcal isolates that exhibited a positive Quellung reaction using commercial type specific antisera obtained from Statens Serum Institute, Copenhagen, Denmark were assigned a serotype designation [7]. Strains that were susceptible to optochin but which failed to serotype, were tested further using AccuProbe™ *Streptococcus pneumoniae* culture identification test, Gen-Probe, San Diego, CA, to confirm the species identification.

Results

From 2000 to 2013 there were 3243 cases of IPD identified in our database of which 68 (2.1%) were classified as cases of cellulitis. Cellulitis was present on admission in 31 (45%) of the cases. Eight (11.7%) patients had more than one non-contiguous area of skin involved. Table 1 gives the anatomic location of the cellulitis. The most commonly involved areas were leg and periorbital, accounting for 60 % of the total; foot and neck were next accounting for an additional 23.5%. Only one child (7%) had involvement of a lower extremity [that child also had an upper extremity involved] compared with 34 (71%) [p< 0.001] of adults. Two patients had necrotizing fasciitis although their initial presentation was that of cellulitis. Nine of the 16 patients with periorbital cellulitis were children.

Table 2 gives a comparison of demographic and outcome features for those with cellulitis (68 cases) and the larger group with IPD without cellulitis (3177 cases). The only difference between the two groups was hospital stay was longer in the cellulitis group. Analysis of habit data and comorbid illnesses (Table 3) found that hepatitis C (odds ratio and 95% confidence intervals, 2.97 (1.67,5.31)) and systemic lupus erythematosus (7.88 (2.79,22.35)) to be risk factors for cellulitis in patients with IPD. There was no overlap of patients in these two groups. Eight of the 16 cases that presented with cellulitis and hepatitis C also presented with alcoholism. However there was no significant difference between the cellulitis and non-cellulitis groups with respect to a diagnosis of alcoholism.

Table 1. Sites of cellulitis in 68 patients with invasive pneumococcal disease and cellulitis.

Site	No.	%
Leg	25	36.7
Peri-orbital	16	23.5
Foot	9	13.2
Neck	7	10.3
Toe	2	2.9
Face	3	4.4
Arm	2	2.9
Hand	3	4.4
Breast	1	1.5
Abdomen	3	4.4
Sacrum	1	1.5
Shoulder	1	1.5
Wrist	1	1.5
Groin	1	1.5
Buccal mucosa	1	1.5

Table 2. Demographic characteristics and outcomes.

Demographic characteristics; outcomes	Cellulitis	No cellulitis	p-value
N	68	3177	-
Age (year), mean (SD)	42.7 (26.7)	43.4 (26.1)	0.814
5 years or younger, n(%)	12 (17.6)	518 (16.8)	0.848
Male	40 (58.8)	1792 (56.8)	0.737
First Nations	9 (25.7)	382 (28.7)	0.704
Residence on presentation/admission			0.391
Home	53 (81.5)	2629 (86.0)	
Lodge/group home	4 (6.2)	107 (3.5)	
Subacute care facility	0	7 (0.2)	
Continuing care facility	0	59 (1.9)	
Homeless in a shelter	3 (4.6)	95 (3.1)	
Homeless not in a shelter	4 (6.2)	79 (2.6)	
Homeless disabled	0	2 (0.1)	
Jail	0	6 (0.2)	
Other	1 (1.5)	73 (2.4)	
Functional status in week preceding presentation/admission			
Walking with no problems	46 (85.2)	2191 (86.4)	
Walking with assistance	8 (14.8)	285 (11.2)	
Bedridden	0	19 (0.8)	
Length of stay (day), median (IQR)	9 (5, 19)	7 (4, 15)	0.041
ICU admission	14 (20.6)	740 (23.3)	0.601
Discharged			
Home	50 (73.5)	1974 (62.1)	0.055
Discharged against medical advice	3 (4.4)	110 (3.5)	0.512
Continuing or long-term care facility (not previously living in LTC)	1 (1.5)	18 (0.6)	0.332
Subacute care facility	3 (4.4)	78 (2.5)	0.240
Died (in hospital)	4 (5.9)	382 (12.0)	0.122

Data are presented as n (%), otherwise stated

Table 3. Habit data and comorbid illnesses.

	Cellulitis (n=68)	No cellulitis (n=3177)	p-value
Current/ former smoker	29 (58.0)	1605 (69.8)	0.072
Alcoholism	13 (19.1)	584 (18.4)	0.877
Illegal drug use	13 (19.1)	424 (13.3)	0.168
Attended day care	3 (25.0)	78 (22.7)	0.740
Cancer within 5 years before ISP infection	3 (4.4)	312 (9.8)	0.136
Cancer > 5 years	3 (4.4)	119 (3.7)	0.741
Transplant - solid organ	0	24 (0.8)	1.000
Transplant - bone marrow	0	24 (0.8)	1.000
CNS[a]	10 (14.7)	370 (11.6)	0.438
Cardiovascular[b]	22 (32.4)	831 (26.2)	0.251
Hematological[c]	5 (7.4)	226 (7.1)	0.813
Diabetes mellitus	6 (8.8)	194 (6.1)	0.310
Cirrhosis	5 (7.4)	129 (4.1)	0.203
Inflammatory bowel disease	1 (1.5)	26 (0.8)	0.437
CRF[d]	3 (4.4)	111 (3.5)	0.516
HIV/AIDS	2 (2.9)	108 (3.4)	1.000
Rheumatoid arthritis	0	61 (1.9)	0.639
SLE[e]	4 (5.9)	25 (0.8)	0.003
Mental Health	6 (8.8)	344 (10.8)	0.598
MSK[f]	10 (14.7)	432 (13.6)	0.792
COPD	5 (7.4)	421 (13.3)	0.154
Hepatitis C	15 (22.1)	276 (8.7)	< 0.001

Data are presented as n (%)
[a]Central nervous system impairment
[b]Cardiovascular disease
[c]Hematological abnormalities
[d]Chronic renal failure
[e]Systematic lupus erythematosus
[f]Musculoskeletal impairment

The serotypes causing IPD with and without cellulitis are given in Table 4. There was no difference in the distribution of serotypes between the two groups. Amongst patients with cellulitis, 25%, 32% and 39% had infection with serotypes in the PCV 7, PCV 13 and PPV23 vaccines respectively.

Table 4. Distribution of pneumococcal serotypes amongst those with cellulitis and no cellulitis Distribution of serotypes comparing cellulitis and no cellulitis patients in the study population.

Serotype	Cellulitis (N=68)		No cellulitis (N=3177)	
	Count	%	Count	%
1	1	1.50	70	2.20
10A	2	2.90	19	0.60
10F	0	0.00	4	0.10
11A	3	4.40	73	2.30
11B	0	0.00	7	0.20
11C	0	0.00	1	0.00
11F	0	0.00	4	0.10
12F	0	0.00	82	2.60
13	0	0.00	14	0.40
14	5	7.40	267	8.40
15A	0	0.00	21	0.70
15B	1	1.50	21	0.70
15C	1	1.50	19	0.60
16F	0	0.00	38	1.20
17F	0	0.00	31	1.00
18A	0	0.00	1	0.00
18B	0	0.00	9	0.30
18C	1	1.50	112	3.50
18F	0	0.00	2	0.10
19A	1	1.50	117	3.70
19F	3	4.40	130	4.10
2	1	1.50	0	0.00
20	2	2.90	58	1.80
21	0	0.00	2	0.10
22A	0	0.00	2	0.10
22F	2	2.90	161	5.10
23A	1	1.50	28	0.90
23B	1	1.50	13	0.40
23F	2	2.90	86	2.70
28A	0	0.00	7	0.20
28F	0	0.00	1	0.00
29	0	0.00	3	0.10
3	3	4.40	181	5.70
31	0	0.00	17	0.50
33A	0	0.00	17	0.50
33F	1	1.50	59	1.90
34	1	1.50	16	0.50
35A	0	0.00	2	0.10
35B	1	1.50	35	1.10
35C	0	0.00	1	0.00
35F	1	1.50	16	0.50
37	0	0.00	2	0.10
38	3	4.40	20	0.60
4	6	8.80	281	8.80
40	0	0.00	1	0.00
41F	0	0.00	1	0.00
42	0	0.00	2	0.10
5	5	7.40	293	9.20
6A	2	2.90	98	3.10
6B	3	4.40	139	4.40
75	0	0.00	1	0.00
7C	0	0.00	2	0.10
7F	3	4.40	117	3.70
8	4	5.90	210	6.60
9L	0	0.00	7	0.20
9N	4	5.90	62	2.00
9V	3	4.40	119	3.70
Not available	0	0.00	2	0.10
Non typable	0	0.00	5	0.10
Non-viable	0	0.00	3	0.10
PCV 7	17	25.00	912	28.70
PCV 13	22	32.40	1237	38.90
PPV 23	27	39.70	1493	47.00

Discussion

This study analysis shows that pneumococcal cellulitis occurs in 2% of patients with IPD and is therefore not nearly as uncommon as earlier literature would suggest [2,3]. Garcia-Lechuz *et al.* [8] found that 2.2% of 3,201 isolates from skin and soft tissue samples were *S. pneumoniae.* Their study differed from ours in that only 4 patients had cellulitis and surgical wound infections, burn wound infections, pyomositis and perineal or scrotal abscesses were sources of the infection. Capdervilla *et al.* [9] found that cellulitis complicated 0.9% of all cases of pneumococcal bacteremia and 3.2% of community acquired bacteremia at their centre from 1984-2001. They also noted that a concomitant extracutaneous focus of infection, especially respiratory tract infections was more frequent in patients with pneumococcal cellulitis than in those with cellulitis due to *Staphylococcus aureus* suggesting hematogenous spread with metastatic cellulitis [9]. This group observed 30 day mortality rates of 10%, 13% and 23% in patients with cellulitis due to pneumococcus, *S. aureus* and *S. pyogenes* respectively. For our study, we found an in hospital mortality rate of 5.9% for the pneumococcal cellulitis patients compared with 12% (p – NS) for the patients with IPD but without cellulitis.

A major finding from our study is that SLE and hepatitis C are independent risk factors for developing cellulitis in the setting of invasive pneumococcal disease. The association of pneumococcal soft tissue infection and SLE was noted in 1991 by Di Nubile *et al.* [10] when they described 12 cases of pneumococcal soft tissue infections, 50% of whom were bacteremic and 5 of whom had SLE. In 2006 Sabio *et al.* [11] reported a case of soft-tissue pneumococcal infection in one of their patients with SLE and reviewed the literature to that point. They found that 11/46 (24%) of patients with pneumococcal soft tissue infections had SLE and the majority (9 cases), of these had involvement of the face, scalp, upper chest or breast. They indicated that there are multiple reasons for the increased susceptibility of SLE patients to pneumococcal cellulitis – these include immunosuppressive therapy, hypocomplementemia, acquired hyposplenism and homozygosity for R131 allele which determines a low binding affinity of IgG2 for bacterial capsules [11]. These factors certainly predispose to invasive pneumococcal disease but may not be the entire explanation for the propensity to cellulitis. In our study 29 patients with IPD had SLE and 4 of the 29 (13.7%) had cellulitis.

A new finding from our study is that hepatitis C is a risk factor for pneumococcal cellulitis. In all likelihood it is cirrhosis and not hepatitis C that is the risk factor. In a study of patients with chronic hepatitis C undergoing treatment with pegylated interferon alpha and ribavirin it was cirrhosis and not neutropenia that was associated with the development of infection [12]. Patients with cirrhosis have many alterations in bacterial host defense mechanisms including impairment of macrophage Fc_{γ} receptor mediated clearance of antibody coated bacteria, deficiency in complement system, down regulation of monocyte HLA-DR expression and depressed neutrophil phagocytic and intracellular killing [13].

It is interesting to note that we did not find any particular pneumococcal serotype association with cellulitis.

However, we did find a striking difference in the site of the cellulitis in children compared with adults. The former had infrequent

involvement of the lower extremities, 7%, compared with 71% for adults. Skin and soft tissue structure infections are common in children and account for 25% of pediatric clinical encounters [14]. Larru and Gerber in a review of cutaneous bacterial infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* state that cellulitis most commonly occurs in the lower extremities preceded by clinically unapparent local skin trauma [14]. Clearly then pathogenesis of the cellulitis plays a role but undoubtedly there are other factors as well.

Our study has a major strength in that we were able to compare a large number of patients with and without cellulitis in the setting of invasive pneumococcal disease. This is also a limitation in that we only studied the subset of patients with invasive pneumococcal disease. Nevertheless a number of important lessons emerge from this study.

Acknowledgements

We wish to thank Ibrahim Quazi and Lilly Yusho for data management and Pfizer Canada for a grant-in-aid. Thanks to Dr. James Kellner, University of Calgary who participated in the Southern Alberta portion of the study. We are grateful to Carol Mangan RN for data collection.

References

1. Connio A (1917) Diplococcal erysipelas with septicemia. *La Reforma Medica* 33: 709 -12.
2. Sabio JM, Vargas JA, Jiménez-Alonso J (2006) Pneumococcal cellulitis in a patient with systemic lupus erythematosus: a case report and review. *Lupus* 15: 54-57.[Crossref]
3. Parada JP1, Maslow JN (2000) Clinical syndromes associated with adult pneumococcal cellulitis. *Scand J Infect Dis* 32: 133-136.[Crossref]
4. Canada Communicable Disease Report (2000) Case definitions for diseases under national surveillance-Health Canada, 26 S3:51.
5. Swartz MN (2004) Clinical practice. Cellulitis. *N Engl J Med* 350: 904-912.[Crossref]
6. Facklam RR, Washington JA(1991) Streptococcus and related catalase-negative gram-positive cocci. In: Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ (Eds.), Manual of clinical microbiology, (5thedn), American Society for Microbiology, Washington, DC, 238-257.
7. Lund R, Henrichsen J (1978) Laboratory diagnosis, serology and epidemiology of Streptococcus pneumonia. In:Bergan T, Norris JR (Eds.), Methods in Microbiology, vol.12. Academic Press, Inc., New York, NY, 241-262.
8. Garcia-Lechuz JM, Cuevas O,Castellares C, Perez-Fernandez C, Cercenado E, et al. (2007) Spanish Pneumococcal Study Network. Streptococcus pneumonia skin and soft tissue infections: characterization of causative strains and clinical illness. *Eur J Clin Microbiol Infect Dis* 26: 247-53.[Crossref]
9. Capdervilla O, Grau I, Vadillo M, Cisnal M, Pallares R (2003) Bacteremic pneumococcal cellulitis compared with bacteremic cellulitis caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. *Eur J Clin Microbiol Infect Dis* 22: 337-44. [Crossref]
10. DiNubile MJ1, Albornoz MA, Stumacher RJ, Van Uitert BL, Paluzzi SA, et al. (1991) Pneumococcal soft-tissue infections: possible association with connective tissue diseases. *J Infect Dis* 163: 897-900.[Crossref]
11. Sabio JM, Vargas JA, Jiménez-Alonso J (2006) Pneumococcal cellulitis in a patient with systemic lupus erythematosus: a case report and review. *Lupus* 15: 54-57.[Crossref]
12. Striki A, Manolakopoulos S, Deutsch M, Mela M, Kalafateli M, et al. (2014) Cirrhosis but not neutropenia is associated with the development of infection in patients with chronic hepatitis C undergoing treatment with pegylated interferon-alpha and ribavirin. *J Viral Hepat* 21: 624-632.[Crossref]
13. Fernández J, Gustot T (2012) Management of bacterial infections in cirrhosis. *J Hepatol* 56: S1-12.[Crossref]
14. Larru B, Gerber JS (2014) Cutaneous bacterial infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* in infants and children. *Pediatr Clin North Am* 61: 457-478.[Crossref]