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Note

Cellulitis Complicating Lymphoedema

P.C.Y. Woo, P.N.L. Lum, S.S.Y. Wong, V.C.C. Cheng, K.Y. Yuen

Abstract In ten hospitalised patients with cellulitis complicating lymphoedema encountered over a 3-year period (1996–1998), the underlying diseases were carcinoma of the cervix ($n=4$), uterus ($n=1$), vagina ($n=1$), breast ($n=2$) and nasopharynx ($n=1$), and retroperitoneal squamous cell carcinoma ($n=1$). Three of the ten patients had positive blood cultures, compared to none of the 20 age-matched, sex-matched controls hospitalised for cellulitis without lymphoedema. The mean duration of fever, tachycardia and cellulitis was significantly longer in patients with lymphoedema than in those without ($P<0.05$, $P<0.05$, and $P<0.005$ respectively). Early treatment initiated by patients themselves may help stop bacterial replication in the initial stages and minimise further damage to the lymphatic system.

Introduction

Lymphoedema has recently been revealed to be the most important risk factor in the development of recurrent cellulitis [1]. Of the known predisposing factors for lymphoedema and recurrent cellulitis, which include radical hysterectomy, mastectomy, nodal resection, radiotherapy and lymphatic filariasis, only gynaecological malignancies and breast carcinoma treated surgically with or without radiotherapy have been extensively reviewed [2–4]. Although cellulitis is presumed to be caused mainly by non-group A streptococci, in more than 80% of cases the pathogen is not identified [2, 5], and the pathogenesis of recurrent episodes of cellulitis is poorly understood. Moreover, no case-control studies have been conducted to ascertain whether there are differences in the clinical course and outcome between patients with cellulitis and lymphoedema and patients with cellulitis but no lymphoedema. The management of patients with recurrent cellulitis usually consists of antibiotic prophylaxis and therapy with beta-lactam agents, however these strategies are empirically based. A group in Taiwan showed recently that monthly benzathine penicillin was not effective in preventing further episodes of cellulitis in patients with lymphoedema and streptococcal cellulitis [6]. Thus, the optimal treatment and prophylaxis in these patients remains to be determined.

In this report, we summarise our observations in hospitalised patients with cellulitis complicating lymphoedema referred to our infectious disease consultation service over a period of 3 years. The characteristics and outcome in these patients and in hospitalised patients with cellulitis but no lymphoedema were also compared.

Materials and Methods

Patients. The patients with cellulitis complicating lymphoedema included in this study were selected retrospectively from a total of 4108 hospitalised patients referred to our infectious disease consultation service over a 3-year period (1996–1998) in a tertiary care teaching hospital. For each case two age-matched (no more than 5 years difference between case and control), sex-matched controls at the same hospital were randomly selected; these control patients were also referred to our infectious disease consultation service within the same 3-year period and had cellulitis as the discharge diagnosis. Data on the duration of fever, tachycardia and cellulitis was collected only for the inpatient period. Patients receiving glucocorticoids and cytotoxic agents within 3 months from the date of admission were excluded from the study, since cellulitis in these patients is prolonged as a result of drug-induced immunodeficiency.

Definitions. Fever was defined as either two oral temperature measurements of more than 38 °C during a 24-h period or a single oral temperature of more than 38.5 °C [7]. Tachycardia was defined as a heart rate of more than 90 beats per minute [7]. Follow-up blood cultures were those taken at least 2 days after administration of antibiotics for the investigation of prolonged fever.

Statistical Analysis. Comparisons were made between the characteristics and outcome of patients having cellulitis with and without lymphoedema. The chi-square test was used for analysis of categorical variables and the unpaired Student's *t* test for analysis of continuous variables. A P value <0.05 was considered statistically significant.

P.C.Y. Woo, P.N.L. Lum, S.S.Y. Wong, V.C.C. Cheng, K.Y. Yuen (✉)
Division of Infectious Diseases, Department of Microbiology, The University of Hong Kong, University Pathology Building, Queen Mary Hospital, Hong Kong
e-mail: microgen@hkucc.hku.hk

Results and Discussion

The underlying diseases, gender, organisms recovered and response to antibiotics in the ten patients with cellulitis complicating lymphoedema observed during the 3-year period were similar to those reported in the literature (Table 1). Most patients (8/10) had gynaecological malignancies or breast cancer. In all of the three patients with positive blood cultures non-group A streptococci were isolated. This is in line with the findings of other groups, who also reported a preponderance of non-group A beta-haemolytic streptococci in patients with cellulitis complicating lymphoedema [2, 5]. Although only a minority of the patients with lymphoedema had positive blood cultures, in the control group without lymphoedema no blood cultures were positive. This can probably be attributed to the fact that patients with lymphoedema have relatively higher initial microbial counts and abnormal bacterial filtration systems in their regional lymph nodes after dissection of lymphatic vessels or radiotherapy for underlying diseases, allowing bacteria in the skin and soft-tissue access to the systemic circulation at an early stage. None of our patients or those reported in the literature died as a result of the cellulitis.

As in many other infections, at least part of the damage in cellulitis complicating lymphoedema is the consequence of immunopathological processes. All follow-up cultures obtained from the patients were negative, showing that the infections were well under control. However, the patients with lymphoedema had prolonged systemic and local inflammatory responses. The prolonged systemic inflammatory response was evident from the statistically significant longer duration of fever and tachycardia and the higher number of patients with fever and tachycardia for 6 or more days, whereas the prolonged local inflammatory response was evident from the statistically significant longer duration of cellulitis and the higher number of patients with cellulitis for 10 or more days (Table 2). In patients without lymphoedema, bacterial components released from bacteria killed by phagocytosis and/or antibiotics are eliminated efficiently by the lymphatic drainage. In patients with lymphoedema, however, stagnation of lymph may lead to impaired elimination of these bacterial components, which are important triggers of the cytokine cascade and local and systemic inflammatory responses. This results in persistent fever, tachycardia and cellulitis, and the persistent inflammation leads to further lymphatic damage, greater stagnation of lymph

Table 1 Clinical characteristics, laboratory findings and treatment in ten patients with cellulitis and lymphoedema

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Gender	F	F	F	F	F	M	F	F	F	F
Age	60	54	51	44	67	82	54	72	46	69
Underlying disease and treatment	Ca uterus, total hysterectomy, radiotherapy	Ca cervix, total hysterectomy, radiotherapy	Ca cervix, Werthim's hysterectomy, radiotherapy	Ca cervix, Werthim's hysterectomy	Ca vagina, radiotherapy	retroperitoneal SCC, surgical resection, chemotherapy	Ca cervix, total hysterectomy, radiotherapy	Ca breast, mastectomy, radiotherapy	Ca nasopharynx, radiotherapy	Ca breast, mastectomy, radiotherapy
Site of cellulitis	lower limb	lower limb	lower limb	lower limb	vulva	lower limb	lower limb	upper limb	neck	upper limb
Admission leukocyte count ($\times 10^9$/l)	5.1	6.3	6.6	6.7	17.9	9.0	14.8	7.5	11.0	7.2
Admission neutrophil count ($\times 10^9$/l)	4.2	3.3	5.3	6.3	15.9	8.2	12.1	5.7	10.0	6.7
Admission lymphocyte count ($\times 10^9$/l)	0.4	2.5	0.8	0.4	1.3	0.5	1.8	1.1	0.4	0.4
Blood culture on admission	NG	NG	NG	*Streptococcus agalactiae*	NG	NG	*Streptococcus agalactiae*	NG	NG	group G streptococcus
Antibiotic therapy	amoxicillin/clavulanic acid	penicillin G	cefazolin	penicillin G	penicillin G	amoxicillin/clavulanic acid	penicillin G	ampicillin, cloxacillin	penicillin G	penicillin G
Follow-up blood culture	NG	ND	ND	NG	ND	ND	NG	NG	NG	NG
Duration of fever (days)	11	0	0	10	1	1	8	2	3	2
Duration of tachycardia (days)	11	0	0	4	0	10	8	2	2	2
Duration of cellulitis (days)	13	19	37	21	16	25	14	30	5	10

Ca, carcinoma; SCC, squamous cell carcinoma; NG, no growth; ND, not done

Table 2 Comparison of clinical characteristics and laboratory findings in patients having cellulitis with and without lymphoedema

	Lymphoedema ($n=10$)	No lymphoedema ($n=20$)	P value
Gender (M:F)	1:9	2:18	NS
Median age (range)	57 (44–82)	60 (45–83)	NS
Site of cellulitis (no. of patients)			
Upper limb	2	5	NS
Lower limb	6	15	
Other	2	0	
Findings on admission (mean ± SEM)			
Leukocyte count ($\times 10^9$/l)	9.2 ± 1.3	13.0 ± 1.9	NS
Neutrophil count ($\times 10^9$/l)	7.8 ± 1.2	12.9 ± 2.8	NS
Lymphocyte count ($\times 10^9$/l)	1.0 ± 0.2	1.4 ± 0.2	NS
Monocyte count ($\times 10^9$/l)	0.5 ± 0.1	0.7 ± 0.1	NS
Bilirubin (μmol/l)	9.6 ± 1.3	11.9 ± 2.6	NS
ALP (U/l)	83.3 ± 8.9	92.2 ± 5.4	NS
AST (U/l)	31.7 ± 9.5	21.4 ± 2.7	NS
ALT (U/l)	35.3 ± 11.2	23.8 ± 3.4	NS
Albumin (g/l)	40.1 ± 1.3	39.5 ± 1.7	NS
Globulin (g/l)	30.8 ± 2.1	32.8 ± 1.2	NS
Urea (mmol/l)	10.8 ± 3.5	10.0 ± 2.4	NS
Creatinine (μmol/l)	87.8 ± 8.9	118.2 ± 20.1	NS
Duration of fever			
Mean ± SEM (days)	4.5 ± 1.4	1.2 ± 0.3	<0.05
≥6 days (no. of patients)	3	0	<0.01
<6 days (no. of patients)	7	20	
Duration of tachycardia			
Mean ± SEM (days)	3.7 ± 1.2	0.8 ± 0.3	<0.05
≥6 days (no. of patients)	3	0	<0.01
<6 days (no. of patients)	7	20	
Duration of cellulitis			
Mean ± SEM (days)	17.9 ± 3.0	5.9 ± 0.6	<0.005
≥10 days (no. of patients)	9	3	<0.001
<10 days (no. of patients)	1	17	

NS, not significant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; SEM, standard error of mean

and further episodes of cellulitis, resulting in a vicious cycle of recurrent cellulitis.

Immunomodulatory agents such as clindamycin and the macrolides may have a role to play in the treatment of patients with recurrent cellulitis complicating lymphoedema. Beta-lactam agents, in particular penicillin G, have been the mainstay of treatment. However, this treatment is largely empirically based, there being no controlled trials comparing beta-lactams with other groups of antibiotics. Clindamycin and the macrolides have both antibacterial and immunomodulatory activity [8]. Clindamycin has beneficial effects in patients with necrotising fasciitis due to its immunomodulatory activity and inhibitory effect on protein synthesis [9]. Furthermore, we have shown that clarithromycin attenuates the inflammatory response in surgical trauma and chemotherapy-induced mucositis in a guinea pig and a mouse model, respectively [10, 11]. Therefore, after use of beta-lactam agents in the initial phase of treatment, which requires rapid bactericidal action, there may be advantages in the use of clindamycin or macrolides in the latter phase of treatment of recurrent cellulitis complicating lymphoedema. Clinical trials comparing beta-lactam agents and clindamycin or macrolides in the latter phase would thus seem warranted. However, because of the world-wide increase in resistance of streptococci to macrolides, the duration of therapy with beta-lactam agents before switching to macrolides has to be given careful consideration.

Early treatment initiated by the patients themselves may help stop bacterial replication in the initial stages and minimise further damage to the lymphatic system. The mainstay of prophylaxis of recurrent cellulitis complicating lymphoedema has been administration of antibiotics, mainly in the form of monthly benzathine penicillin injections. However, in a recent study on the role of benzathine penicillin in the prophylaxis of recurrent streptococcal cellulitis of the lower legs, monthly benzathine penicillin prophylaxis only benefited patients without predisposing factors for cellulitis, and not those with lymphoedema [6]. We propose a self-medication strategy for early treatment of cellulitis in these patients. Patients enrolled in such a treatment programme could be followed up half-yearly and given a supply of oral antibiotics such as amoxicillin. At the

earliest signs of cellulitis, they could then start taking the antibiotics at the usual dose for 5–7 days. Since in our patient series there was a median time lag of 2 days before patients sought medical help, it is logical to suppose that this self-treatment strategy would stop bacterial replication in the initial stages, thus minimising further lymphatic damage and interrupting the vicious cycle. The optimal treatment and prophylaxis in patients with cellulitis complicating lymphoedema remain to be determined, and the present observations indicate that further studies are warranted.

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References

1. Dupuy A, Benchikhi H, Roujeau JC, Bernard B, Vaillant L, Chosidow O, Sassolas B, Guillaume JC, Grob JJ, Sylvie BG: Risk factors for erysipelas of the leg (cellulitis): case-control study. British Medical Journal (1999) 318:1591–1594
2. Simon MS, Cody RL: Cellulitis after axillary lymph node dissection for carcinoma of the breast. American Journal of Medicine (1992) 93:543–548
3. Chmel H, Hamdy M: Recurrent streptococcal cellulitis complicating radical hysterectomy and radiation therapy. Obstetrics and Gynecology (1984) 63:862–864
4. Dankert J, Bouma J: Recurrent acute leg cellulitis after hysterectomy with pelvic lymphadenectomy. British Journal of Obstetrics and Gynaecology (1987) 94:788–790
5. Baddour LM, Bisno AL: Non-group A beta-hemolytic streptococcal cellulitis. Association with venous and lymphatic compromise. American Journal of Medicine (1985) 79:155–159
6. Wang JH, Liu YC, Cheng DL, Yen MY, Chen YS, Wang JH, Wann SR, Lin HH: Role of benzathine penicillin G in prophylaxis for recurrent streptococcal cellulitis of the lower legs. Clinical Infectious Diseases (1997) 25:685–689
7. Nystrom P-O: The systemic inflammatory response syndrome: definitions and aetiology. Journal of Antimicrobial Chemotherapy (1988) 41, Supplement A:1–7
8. Ritts RE: Antibiotics as biological response modifiers. Journal of Antimicrobial Chemotherapy (1990) 26, Supplement C:31–36
9. Bisno AL, Stevens DL: Streptococcal infections of skin and soft tissues. New England Journal of Medicine (1996) 334:240–245
10. Woo PCY, Chow LWC, Ma ESK, Yuen KY: Clarithromycin attenuates the inflammatory response induced by surgical trauma in a guinea pig model. Pharmacological Research (1999) 39:49–54
11. Woo PCY, Ng WF, Leung HCH, Tsoi HW, Yuen KY: Clarithromycin attenuates cyclophosphamide-induced mucositis in mice. Pharmacological Research (in press)