Lymphology 51 (2018) 47-53

PECULIAR CLINICAL FEATURES OF CELLULITIS IN PERIPHERAL LYMPHEDEMA

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ABSTRACT

Although the occurrence of cellulitis in lymphedema (LE) is believed to be an infection-related event, many findings in its clinical course seem to suggest that it is unlikely to be an infection. Therefore, we tried to clarify the specific features of cellulitis in LE. In-hospital courses of cellulitis obtained from medical charts were reviewed in the patients with leg LE (LE; 24 patients, 72 admissions), chronic venous insufficiency (CVI; 28 patients, 29 admissions), and leg cellulitis secondary to wound infection without underlying disease (N; 42 patients, 42 admissions). The patients with LE complained of less local pain (peak numerical scale; LE: 1.4 ± 1.7, CVI: 4.1 ± 2.5, N: 3.2 ± 2.0, $p < 0.0001$), showed an abnormally higher peak procalcitonin level (LE: 33.8 ± 34.8 (N = 7), CVI: 2.9 ± 5.8 (N = 8), N: 0.4 ± 0.6 (N = 10), $p < 0.05$), and required fewer antibiotics (LE: 1.1 ± 0.3, CVI: 1.8 ± 0.9, N: 1.5 ± 0.9, $p < 0.0001$). These findings suggested that the occurrence of cellulitis in LE seems unlikely to be an infection-related type of cellulitis similar to that found in CVI.

Keywords: lymphedema, cellulitis, chronic venous insufficiency, infection, antibiotics, procalcitonin, pain

Lymphedema (LE) is known as an independent risk factor for cellulitis (1,2). Cellulitis in LE has been considered as a primary infection or acute exacerbation of dermato-lymphangio-adenitis (DLA), a condition of chronic bacterial colonization in the tissue in which lymphatic transport is compromised. In acute cases of DLA, it is also known that patients' health can be complicated by septicemia with as much as 26% of patients affected as a result (3). On the other hand, greater consumption of fatty foods (4), higher serum high-sensitivity C-reactive protein level (5), and extreme exercises or labor (6), all which seem irrelevant to infections, have been reported to be risk factors for cellulitis in LE. In this study, we compared the in-hospital courses of cellulitis in leg LE with those in chronic venous insufficiency (CVI), i.e., another independent risk factor for leg cellulitis, and leg cellulitis secondary to the infected wound in otherwise healthy patients, and clarified these differences in order to discuss the possible causes of cellulitis in LE.

METHODS

This retrospective study was approved by the Institutional Review Board of Yamaguchi University Hospital (Center for Clinical Research, Ube, Yamaguchi, Japan), and the

TABLE 1
Patient Characteristics at the Time of Admission

	LE	CVI	N
Number of patients	24	28	42
Age at the time of admission (years)	65 ± 18	72 ± 14 *	53 ± 21
Sex (male:female)	8:16	10:18	22:20
BMI at the time of admission (kg/m^2)	25 ± 4	27 ± 9	26 ± 7
Diagnosis	Primary LE 5 Secondary LE 17	PVI 5 PTS 1 FVI 22	N.A.
	Stage I 0 II 19 III 5	C3 12 C4 9 C5 3 C6 4	
Disease duration at the time of admission (years)	14 ± 15	Unclear	N.A.
Number of admissions	72	17	42
Number of admissions per patient	3.0 ± 4.3 †*	1.0 ± 0.2	1.0 ± 0.0

LE: lymphedema, CVI: chronic venous insufficiency, BMI: body mass index, PVI: primary venous insufficiency, PTS: post-thrombotic syndrome, FVI: functional venous insufficiency, N.A.: not applicable, N.S.: not significant; C 3-6, C-class in Clinical, Etiology, Anatomy, Pathophysiology classification (7,8), †: $p < 0.05$ vs. CVI; *: $p < 0.05$ vs N.

need for individual patient consent was waived. The subjects included in the current study were patients who met the following criteria: (A) Patients with leg LE or CVI, which was defined as chronic venous disease with the symptom of C3 or greater in Clinical, Etiological, Anatomical, Pathophysiological classification (7,8), whose diagnoses were made in our clinic; and (B) Patients who had a history of admission to Yamaguchi University Hospital because of the presence of cellulitis in any affected leg.

Twenty-four patients with LE and 28 patients with CVI met the criteria. For control comparison, subjects who met the following criteria (N) were also included in the study: (A) Patients who had no underlying diseases; and (B) Patients who had a history of admission to Yamaguchi University Hospital because of cellulitis secondary to wound infection. Forty-two patients met these criteria. The patients' characteristics are summarized in *Table 1*. Their medical charts between January 2004 and December 2016 were reviewed for the information regarding the symptoms of cellulitis, the results of blood tests, and treatment details during the admission. In this study, only cellulitis that affected more than half of a leg was included, namely, cellulitis occurring in a limited area, such as the foot, was excluded.

Statistical Analysis

The results are expressed as mean ± standard deviation, unless otherwise indicated. In order to test the differences in data between patients with LE, CVI with/without an infected wound, and N, the Kruskal-Wallis test was used. The Mann-Whitney *U* test was used for multiple comparisons. Statistical analyses were performed using

JMP 11.0 (SAS Institute, Cary, NC, USA). A p-value of < 0.05 was considered significant.

RESULTS

From medical charts, 72 admissions in the LE group, 29 admissions in the CVI group, and 42 admissions in the N group were confirmed (*Table 1*). The admissions were more frequent for LE (number per patient; LE: 3.0 ± 4.3, CVI: 1.0 ± 0.2, N: 1.0 ± 0.0; $p < 0.001$). Because many patients with LE were admitted to other hospitals as well, the frequency might be greater. The in-hospital conditions are summarized in *Table 2*. Approximately one-third of the patients with LE were admitted to our department (Department of Surgery, Division of Vascular Surgery); however, a considerable number of patients with LE were also admitted to the departments in which they had causative oncologic surgery.

Symptoms

No patient was affected by necrotizing cellulitis in this series. One patient each in the LE group and the N group were treated in an intensive care unit. Amongst the 72 admissions in the LE group no infected wounds were confirmed. On the other hand, external wounds, including venous leg ulcers, were confirmed in 12 cases (41%) amongst the 29 admissions in the CVI group. Hereafter, CVIs with/without external wound were separately assessed (CVIw+, and CVIw-, respectively). Peak fever was higher in the LE group, compared to that in the CVIw+/- and N groups ($p < 0.0001$). Febrile (> 37.5°C) duration in the LE group was not different from that in the CVIw- group. Local pain, both in terms of intensity expressed on the peak numerical rating scale, and duration, was less in the LE group compared to that in the CVIw+/- and N groups ($p < 0.0001$, each). Among 72 admissions in the LE group, patients did not complain of local pain in 40 cases (56%) while this was seen in 1 case (6%) in the CVIw- group, 0 cases (0%) in the CVIw+ group, and 3 cases (7%) in the N group ($p < 0.0001$).

Blood Tests

Peak white blood cell counts (WBC) were similar in all groups; however, peak neutrophil count was higher in the LE group than that in the CVIw+/- and N groups ($p < 0.0001$). The time for WBC and CRP levels to normalize in the LE group was shorter than that in the CVIw- group. Procalcitonin (PCT) levels were tested in only 7 cases in the LE group, 4 cases in the CVIw- group, 4 cases in the CVIw+ group, and 9 cases in the N group, because the examination had become available recently. The peak PCT level was significantly and abnormally higher in the LE group, compared to that in the CVIw- and N groups. Clinical courses in 6 patients with LE in whom peak PCT > 2.0 ng/mL, i.e. cut-off value for severe sepsis, were recorded are summarized in *Table 3*. One patient was transferred to the intensive care unit because of shock; a bacteria-positive blood culture from another hospital was obtained for this patient. However, interestingly, 4 patients became afebrile within 3 days after intravenous single cephem or penicillin administration and were discharged home between days 4 to 6. Only one bacteria-positive blood culture was confirmed in the LE group, which revealed the presence of the *Streptococcus dysgalactiae* strain. All blood cultures were negative in the CVI group. In the N group, blood culture was positive in 2 cases in which *Enterococcus faecalis* and methicillin-resistant *Staphylococcus epidermidis* were confirmed respectively.

Treatments

The duration of antibiotic treatment was shorter in the LE group than in the CVIw+/-, and N groups ($p < 0.0001$). Antibiotic selection did not differ between

TABLE 2
In-Hospital Condition

	LE	CVI (without infected wound)	CVI (with infected wound)	N
Number of admissions	72	17	12	42
Admitted department				
Surgery (Division of Vascular Surgery)	21 (29%)	7 (41%)	4 (33%)	0
Gynecology	34 (47%)	0	0	0
Urology	3 (4%)	0	0	0
Dermatology	4 (6%)	7(41%)	6 (50%)	40 (95%)
Orthopedics	2 (3%)	2 (12%)	1 (8%)	2 (5%)
Other	8 (11%)	1 (6%)	1 (8%)	0
Symptoms				
Presence of infected leg wound	0	0	12 (100%)	42 (100%)
Peak fever (°C)	38.8 ± 0.9 †‡*	37.7 ± 0.6 ‡	38.2 ± 0.6 *	37.7 ± 0.8
Febrile duration (days)	1.8 ± 1.1 ‡*	2.3 ± 2.3 ‡	4.1 ± 3.3 *	1.7 ± 2.5
Peak numerical rating scale	1.4 ± 1.7 †‡*	3.7 ± 2.5	4.7 ± 2.6	3.2 ± 2.0
Duration complaining of pain (days)	2.7 ± 2.4 †‡*	6.3 ± 3.3	8.1 ± 4.3	6.5 ± 4.5
Blood tests				
Peak WBC ($\times 10^6$/L)	12152 ± 5116	12082 ± 4377	12266 ± 4117	12202 ± 4080
Peak neutrophil count (%)	89.5 ± 7.5 †‡*	77.7 ± 11.6	78.4 ± 6.5	80.0 ± 8.7
Time to WBC normalized (days)	2.1 ± 1.9 †*	4.3 ± 4.3	5.3 ± 5.4	4.8 ± 5.9
Peak CRP (mg/dL)	16.1 ± 10.6 *	14.3 ± 12.8	18.0 ± 8.4 *	10.7 ± 8.6
Time to CRP normalized (days)	7.5 ± 3.8 †	11.3 ± 4.6 *	11.1 ± 7.3	8.0 ± 6.4
Peak procalcitonin (ng/mL)	33.8 ± 34.8 (N = 7) †*	1.5 ± 2.5 (N = 4)	4.3 ± 8.1 (N = 4)	0.4 ± 0.6 (N = 9)
Positive blood culture	1 (5%; N = 19)	0 (0%; N = 2)	0 (0%; N = 6)	2 (20%; N = 10)
Treatments				
Duration of antibiotic use (days)	6.3 ± 3.0 †‡*	10.5 ± 5.2	12.7 ± 5.9	10.1 ± 5.4
Administrated antibiotics				
Cefem/penicillin	65 (90%)	14 (82%)	12 (100%)	38 (90%)
Cefazolin	11 (15%)	7 (41%)	4 (33%)	30 (71%)
Flomoxef	39 (54%)	3 (18%)	0 (0%)	0 (0%)
Carbapenem	8 (11%)	3 (18%)	5 (36%)	9 (21%)
Quinolone	1 (1%)	1 (6%)	0 (0%)	2 (5 %)
Others	4 (6%)	3 (18%)	4 (33%)	8 (19%)
Single agent:combination or alteration	67:5 †‡*	11:6	5:7	27:15

LE, CVI, *: as in Table 1, N: patients with cellulitis secondary to wound infection without underlying disease, WBC: white blood cell count, CRP: C-reactive protein level, †: P < 0.05 vs. CVI without infected wound; ‡: P < 0.05 vs. CVI with infected wound.

TABLE 3
LE With an Abnormally High Peak Procalcitonin Level

	Age	Sex	Diagnosis	Peak PCT (ng/mL)	Antibiotics given	Fever alleviated	Discharge	Note
1	90	F	Secondary LE	87.96	CEZ i.v.	Day 3	Day 5	
2	18	M	Primary LE	71.43	ABPC/SBT, GM i.v.	Day 2	Day 13	Prolonged admission for examination.
3	46	M	Primary LE	45.13	MEPM, VCM,CLDM i.v.	Day 2	Day 14	Admitted to the emergency department due to shock and septicemia (GPC).
4	67	M	Primary LE	13.64	CEZ i.v.	Day 3	Day 6	
5	53	F	Secondary LE	10.34	FMOX i.v.	Day 1	Day 5	
6	71	M	Secondary LE	7.55	ABPC/SBT, GM i.v.	Day 2	Day 4	

LE, CVI, *: as in Table 1, CEZ: Cefazolin, ABPC: Ampicillin, SBT: Sulbactam, GM: Gentamicin, FMOX: Flomoxef, MEPM: Meropenem, VCM: Vancomycin, CLDM: Clindamycin, GPC: Gram positive cocci.

groups. However, the treatment was completed with a single type of antibiotic in 67 cases (93%) in the LE group, while combination and/or alteration of antibiotics was required because of superinfection and/ or microbial substitution in 6 cases (33%) in the CVIw- group, 7 cases (58%) in the CVIw+ group, and 15 cases (36%) in the N group ($p < 0.0001$).

DISCUSSION

In this study, significant differences between LE and other groups were found in terms of peak fever, local pain, peak neutrophil count, peak PCT level, and response to antibiotic treatments.

Because the duration from the onset of cellulitis to the clinic visit was not precisely recorded in a majority of charts, the peak fever and peak neutrophil count, etc., may not accurately represent the features of cellulitis in LE. However, an absence of local pain was considered to be one specific feature of LE. Bacterial infection normally causes pain because bacteria can directly stimulate nociceptor neurons, in addition to the stimuli caused by inflammatory mediators (9). In the current study, more than 90% of CVIw+/- and N patients complained of local pain. Although it was not expressed by the numerical rating scale, these patients complained of more pain when they stood up or walked. On the other hand, more than half of the patients with LE did not complain of local pain. Since local pain between the CVIw+ and CVIw- groups were similar, the local pain did not seem to be caused by the wound and was instead likely caused by the infection.

Among a considerable number of patients in the CVIw+/- and N groups, combination and/or alteration of antibiotics was required because of superinfection and/or microbial substitution. This may be common in the current antibiotic treatment regimens. For instance, it is reported that the initial antibiotic treatment failure rate is 16.6% in acute skin and skin structure infection, and

34.1% in chronic or ulcerative infections, suggesting the presence of antibiotic-resistant bacteria (10). However, in the LE group, 93% of cases could be managed using a single antibiotic (mostly cephem or penicillin).

PCT level is known as a good indicator of bacterial infection (11). PCT levels greater than 2.0 ng/mL may be indicative of severe sepsis while local bacterial infection does not induce PCT normally (12,13). Despite abnormally high PCT levels, however, single intravenous cephem antibiotics were enough to manage cellulitis in a certain number of patients with LE. These patients were discharged home within 4-6 days, which is an unlikely course if severe sepsis were to be present. It is currently known that a high PCT level does not necessarily indicate bacterial infection (14) although it can be observed in conditions such as cardiogenic shock, cardio-pulmonary resuscitation, sterile pancreatitis, and rhabdomyolysis in which damage associated with molecular patterns (DAMPs) increases (15).

Lymphedema, i.e., lymph stasis due to a low output failure of the lymphovascular system (16), induces chronic inflammation due to uncontrolled responses of macrophages and CD4+ cells (17,18). It has been demonstrated that DAMPs, such as high-mobility group box 1 and heat shock protein 70, are chronically upregulated (19) and the oxidative stress is increased (20) in human lymphedematous tissues. As a result, we can hypothesize that, at least in part, cellulitis in LE could potentially be related to an acute exacerbation of this chronic condition, as seen in acute-on-chronic liver failure (ACLF) (21) rather than it being a simple infection. The mechanism of ACLF is considered to be related to pathogen-associated molecular patterns (PAMPs) released from the bacteria, although not from direct infection, DAMPs, or increased oxidative stress. This hypothesis adequately explains the absence of pain, abnormally high PCT levels, and the absence of antibiotic resistance in cellulitis in LE. Even a high peak neutrophil level could be explained because DAMPs activate human polymorphonuclear neutrophils and cause sterile systemic inflammatory response syndrome even when it is initiated as local immune responses (22). The specific risks for cellulitis in LE, i.e., greater consumption of fatty foods and extreme exercise or labor, both of which are seemingly irrelevant to infections, can also be explained by this hypothesis. This is because an elevated fatty acid level can increase stress towards the endoplasmic reticulum and hence induce DAMPs (23,24). Similarly, intense physical exercise enhances the production of reactive oxygen species (25).

Limitations

In addition to this being a single-center retrospective study, patients were also admitted to various departments in which protocols for treatments and examinations were different. All of these factors may have caused inconclusive results. DLA is often argued in cases of filarial lymphedema (26). However, in Japan we do not have a high incidence of filariasis, and we cannot determine whether cellulitis in LE in the current study was truly acute DLA.

CONCLUSIONS

In the current study we found specific clinical features of cellulitis in LE when compared to those in cellulitis in CVI and cellulitis secondary to wound infection. These results suggest that cellulitis in LE may not be a simple bacterial infection and also that it may be related to other mechanisms as well.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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