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COUNTERPOINT

CELLULITIS AND BACTERIA IN PERIPHERAL LYMPHEDEMA

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Counterpoint to the article: *Peculiar Clinical Features of Cellulitis in Peripheral Lymphedema,* by K. Suehiro, N. Morikage, K. Ueda, M. Samura, Y. Takeuchi, T. Nagase, T. Mizoguchi, K. Hamano.

Keywords: lymphedema, cellulitis, chronic venous insufficiency, infection, antibiotics, procalcitonin, pain, dermato-lymphangio-adenitis

In their article (1), Suehiro and coworkers suggest that although the occurrence of cellulitis in lymphedema 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. They analyzed the in-hospital courses of cellulitis from the medical charts of patients with leg lymphedema, chronic venous insufficiency, and leg cellulitis secondary to wound infection. It was found that lymphedema patients complained of less local pain, showed an abnormally higher peak calcitonin level, and required fewer antibiotics compared to cellulitis in the chronic venous insufficiency. This led the authors to a conclusion that cellulitis in lymphedema is not the host reaction to bacteria. Taken together, the authors negated the role of the bacterial factor; however, they didn't present any other concept that might be the causative factor.

This prompted us to present our own experience, especially in the view that cellulitis is a common complication of partial or total impairment of the lymphatic drainage of lower limb, irrespective whether the cause is local dermatitis, soft tissue trauma, bone fracture, ulcer, ischemic necrosis, diabetic fistula, not to mention oncological lymphadenectomy. They all affect the limb lymphatic system draining the site of the pathological events. The lymphatic system is eliminating free antigens from the destroyed cells, extravasated blood elements, and xenoantigens as bacteria and viruses. In a chronic stage of inflammation, lymphatic collectors and nodes undergo destructive changes bringing about tissue fluid and lymph stasis (*Fig. 1*). As there is impairment of the lymph drainage, microbes penetrating the foot sole, and also those "physiologically" inhabiting limb tissues, cannot be evacuated and neutralized. Thus, the common denominator of cellulitis is presence of bacteria in the inflamed tissue. There is a large body of evidence for the bacterial factor to be responsible for the host inflammatory response in limbs with lymph flow impairment (2-4).

To prove our concept that bacteria are responsible for cellulitis (at present called dermato-lymphangio-adenitis, DLA) we carried out bacteriologic studies of specimens harvested from leg varices, and tissue fluid/lymph and lymphatics in lymphedema. Specimens were harvested in the operating room in sterile conditions, with all appropriate controls, and placed immediately on the Hemoline culture plates and kept at 37°C for days or weeks (*Fig. 2*). We found that saphenous vein varices contained bacterial cells in 40% and controls (cadaver organ donors) in 4%; bacterial DNA (16sRNA) was found in 69%. The majority of bacteria were *S. epidermidis* and *S. aureus*, susceptible to all antibiotics, less to penicillin, lymph and

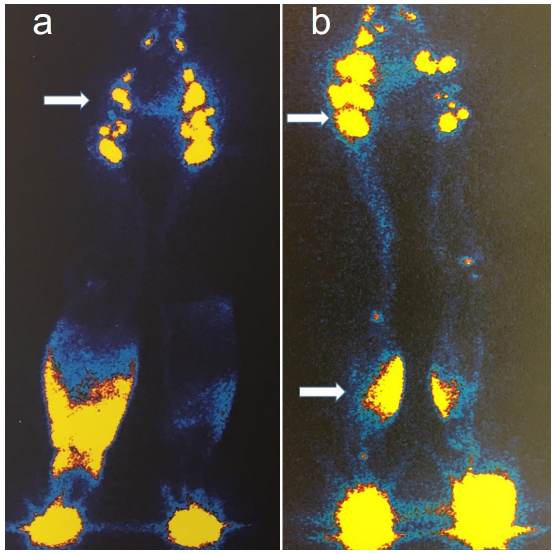

Fig.1. Lymphoscintigrams of limbs showing reaction of the lymphatic system to infection. a. lymphedema of the right lower limb mostly expressed in the calf, arrow points to atrophic inguinal lymph nodes (compare with the contralateral side). b. bilateral venous ulcers (lower arrows), enlargement of the right inguinal nodes.

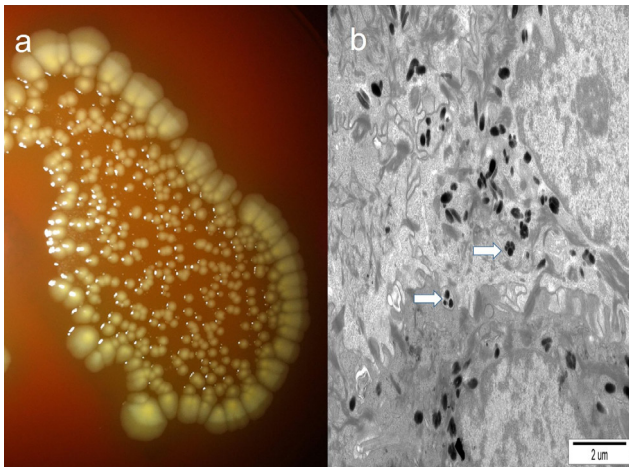

Fig. 2. a. Bacterial colonies from a drop of lymph in cellulitis (DLA) growing on a Hemoline culture plate. b. electronmicrogram of a subcutaneous tissue specimen in lymphedema showing the presence of Cocci in cells and intercellular space (arrows).

epifascial lymphatics contained bacteria in 60% and 33% samples, respectively, and controls in 7%. Most were *S. epidermidis* susceptible to all antibiotics. Moreover, in long-term cultures the persisters (small colony forming variants) were detected (5). Electron microscopical pictures showed in every case with lymph stasis the presence of intracellular and interstitial space Cocci. The conclusion was that cryptic bacteria are present in the lower limb tissues and may play a pathologic role in tissue inflammation.

Also, Staphylococci colonizing vascular bundles and transported to tissues via ischemic limb lymphatics expressed virulence genes at greater frequency than did those

dwelling on the skin surface (6). Another evidence that bacteria are responsible for cellulitis or DLA is the effectiveness of antibiotics on the clinical symptoms (7,8). Long-term penicillin prophylaxis significantly lowers the recurrence rate of cellulitis (DLA).

Recently, we investigated 70 patients with lymphedema of lower limbs stage II-IV with a mean follow-up of 12.6 ± 8.3 (2-30) years and total number of cellulitis (DLA) attacks 297, frequency 4.4 ± 3.7/patient, range/patient 1-20. Benzathine penicillin 1,200,000 u was administered i.m. at 14 day intervals, for 46 ± 41 (range 6-163, median 34) months. Recurrence was observed only in 8 patients with 19 DLA attacks, frequency 2.4/patient, range/patient 1-4 ($p < 0.005$). In conclusion, there were no DLA recurrencies in 89% of patients over a mean of 46 months (unpublished data). Study of other authors corroborate our results (9-12).

In summary, there is enough evidence for the role of bacteria in the inflammatory process in lymphedema. Genotypes of the isolates indicate that these are preferentially Cocci originating from skin surface and also those dwelling in tissues in a persister (cryptic) form. Our findings are of importance as recurrent attacks of cellulitis (DLA) result in increase in limb volume, skin and subcutaneous tissue fibrosis, and other complications as lymph oozing and ulcers. Low dose of long-term penicillin is effective in prevention of the progress of lymphedema.

CONFLICT OF INTEREST AND DISCLOSURE

Author has no actual or potential conflict of interest and no competing financial interests exist.

REFERENCES

1. Suehiro, K, N Morikage, K Ueda, et al: Peculiar clinical features of cellulitis in peripheral lymphedema. Lymphology 51 (2018), 47-53.
2. Cakala, M, WL Olszewski: The response of the lymphatic system to the human skin resident bacteria. Ann. Transplant. 7 (2002), 30-35.
3. Szczêsny, G, B Interewicz B, E Swoboda-Kopec, et al: Bacteriology of callus of closed fractures of tibia and femur. J. Trauma 65 (2008), 837-842.
4. Andziak, P, WL Olszewski, M Moscicka-Wesolowska, et al: Skin own bacteria may aggravate inflammatory and occlusive changes in atherosclerotic arteries of lower limbs. Int. Angiol. 31 (2012), 474-482.
5. Olszewski, WL, M Zaleska, E Stelmach, et al: Cryptic bacteria of lower limb deep tissues as a possible cause of inflammatory and necrotic changes in ischemia, venous stasis and varices, and lymphedema. Surg. Infect. (Larchmt). 16 (2015), 313-322.
6. Olszewski, WL, A Podbielska, H Galkowska, et al: Virulence of Bacteria colonizing vascular bundles in ischemic lower limbs. Surg. Infect. (Larchmt). 17 (2016), 89-93.
7. Olszewski, WL: Episodic dermatolymphangio-adenitis (DLA) in patients with lymphedema of the lower extremities before and after administration of benzathine penicillin: A preliminary study. Lymphology 29 (1996), 126-131.
8. Olszewski, WL, S Jamal, G Manokaran, et al: The effectiveness of long-acting penicillin (penidur) in preventing recurrences of dermatolymphangioadenitis (DLA) and controlling skin, deep tissues, and lymph bacterial flora in patients with "filarial" lymphedema. Lymphology 38 (2005), 66-80.
9. Vignes, S, A Dupuy: Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: A retrospective cohort study. J. Eur. Acad. Dermatol. Venereol. 20 (2006), 818-822.
10. Chlebicki, MP, Oh, CC: Recurrent cellulitis: Risk factors, etiology, pathogenesis and treatment. Curr. Infect. Dis. Rep. 16 (2014), 422.
11. Rob F, J Hercogová: Benzathine penicillin G once-every-3-week prophylaxis for recurrent erysipelas a retrospective study of 132 patients. J. Dermat. Treat. 29 (2018), 39-43.
12. H-M, Li, Y-L, Liu, Y-M, et al: The experience of intramuscular benzathine penicillin for prophylaxis of recurrent cellulitis: A cohort study. J. Microbiol. Immunol. Infection. 50 (2017), 613-618.

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