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Review Article

Cellulitis: making the right diagnosis and its management: a Singapore experience

新加坡的經驗之談：蜂窩性組織炎之正確診斷及治理

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Cellulitis is a common condition that almost all physicians manage at some point in their careers. This condition also contributes to a fair number of referrals to dermatologists in the inpatient and outpatient setting. In this article, we will discuss some differential diagnoses to consider before a label of cellulitis is given. The role of local skin care to promote early recovery as well as the choice of antibiotic are discussed.

蜂窩性組織炎可說是大部份醫生在醫學生涯中都會處理過的常見疾病，當中有不少會被轉介到皮膚科的住院或門診服務。我們將在本文中討論此病確診前所需考慮的其他鑒別診斷、局部皮膚護理對早期復原的好處和簡單討論抗生素之選擇等等。

Keywords: Antibiotics, cellulitis, diagnosis, local skin care

關鍵詞：抗生素，蜂窩性組織炎，診斷，局部皮膚護理

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Introduction

Skin and soft-tissue infections are very common. In Singapore, it was consistently featured in the top ten causes of hospitalization for years 2007 to 2009, and in 2009 there were approximately 9000 admissions for skin and soft tissue infections.[1] In the Singapore General Hospital, there were 1256 admissions in 2010 for skin and soft tissue infections; with the majority (92%) having a diagnosis of cellulitis. Of concern, 26% were admitted for more than 10 days, and 14% were re-admitted within the same year for recurrence of the same condition. Given the substantial impact, it is imperative that strategies

are developed to ensure accurate diagnosis, optimize outcome, antibiotic use, and use of health care resources. Three contemporary problems confounding the clinical evaluation of patients with skin and soft-tissue infections are diagnosis, severity of infection, and pathogen-specific antibiotic resistance pattern. In this article, we will discuss these issues, highlighting them with clinical cases.

Diagnostic challenges

Case 1

A 26-year-old Chinese female sustained a left foot sprain one week prior to admission to hospital. She had visited a Traditional Chinese Medicine (TCM) practitioner the following day after her injury and had topical medicament applied over her left foot. Four days after consultation with TCM practitioner, she started to develop itchiness over her left foot. She also noted redness, swelling and blisters over her left foot. She denied any fever, chills or rigors during that period. She sought treatment at the Accident and Emergency (A&E) department, and was admitted as a case of left foot cellulitis; and started on intravenous amoxicillin/clavulanate.

A dermatological opinion was sought the day following her admission. Clinically she was well with stable vital parameters. She had a sharply demarcated erythema over her left foot. There was localized swelling and a few clear fluid-filled blisters were seen. There was no warmth and minimal tenderness on palpation (Figure 1a). Her inflammatory markers were not significant (WBC 13 X10^9/L, CRP 1.2 mg/L, Procalcitonin <0.12 µg/L). The dermatological diagnosis was contact dermatitis from topical medicaments used by the TCM practitioner. She was given a course of oral and topical steroids. Figure 1b shows the progress four days after treatment, and Figure 1c shows the progress two weeks after treatment.

Case 2

A 21-year-old Chinese female complained of left ankle redness for one week. She noted that it started as "pimple-like swelling" which gradually enlarged over a few days. This was associated with pain especially on ambulation. She had no fever. She had had recurrent admissions since 2008 for similar complaints, and had been treated as cellulitis with courses of antibiotics. She described improvement of condition with bed rest and antibiotics, but never had complete clearance of the lesion. This was her fifth admission to hospital, with a diagnosis of left leg cellulitis on admission and cloxacillin was initiated. A dermatological opinion was sought the day following admission. Clinically she was well, with stable vital parameters. There was a 3 by 4 cm well defined erythematous plaque above her left medial malleolus, which was firm and rubbery in

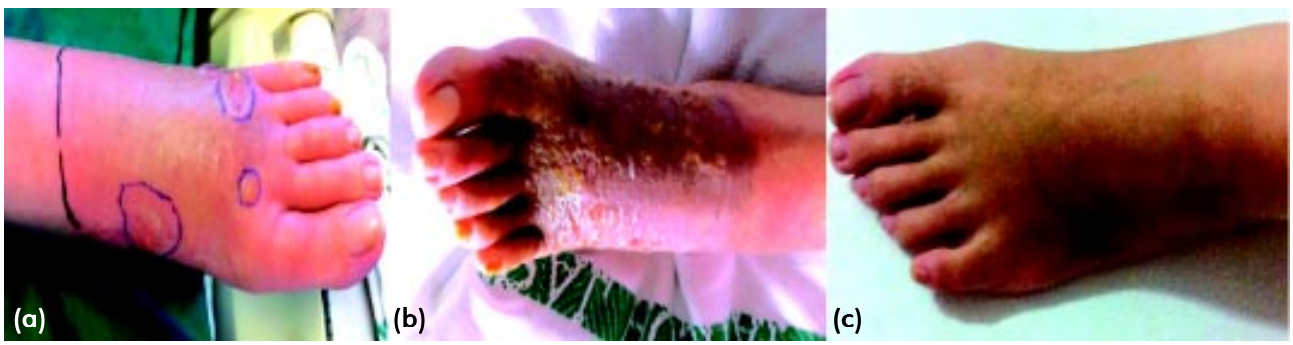

Figure 1. (a) Localized erythema, oedema and tense blisters over left foot dorsum at presentation. (b) Reduced erythema and oedema four days after treatment. (c) Residual localized post inflammatory hyperpigmentation two weeks after treatment.

consistency. It was exquisitely tender to touch. There was no surrounding oedema of her left leg (Figures 2a & 2b).

Her inflammatory markers were unremarkable (WBC 7.4 X10^9/L, CRP 1.5 mg/L).

The dermatological diagnosis was erythema nodosum, which was confirmed with skin biopsy. No triggering factor for her erythema nodosum was identified. She was started on a short course of prednisolone, which showed good response (Figure 2c).

Discussion

An article published by Tay et al demonstrated that the concordance rate between the referring primary physician and dermatologist's diagnosis is only 51.1% in the Singapore General Hospital.[2] A review of dermatological blue letter referrals for Singapore General Hospital in 2010 showed that of 264 cases referred for skin and soft tissue infections, 33 (12.5%) of the cases referred were determined not to be infections by the dermatologists.

Diseases that can mimic cellulitis include acute dermatitis (such as that due to contact with an allergen), panniculitis (such as erythema nodosum), venous stasis dermatitis, deep vein thrombosis and thrombophlebitis. Cellulitis typically presents with erythema, pain, warmth, and oedema.

In severe cases, vesicles, bullae, pustules, and necrosis may be present. It may also present with ascending lymphangitis and regional lymphadenopathy. A report of pruritus or burning, as opposed to pain, is less consistent with cellulitis and should prompt consideration of other diagnoses.[3]

Is it more than just cellulitis?

Case 3

A 49-year-old Chinese male complained of a painful, erythematous swelling over his left leg four days prior to admission. He had low-grade fever of 38 degree Celsius, but did not experience any chills or rigors. He had sought treatment with a general practitioner and was prescribed oral cloxacillin as treatment for cellulitis. He subsequently came to the A&E department as he was concerned that new blisters were forming over his left leg. His inflammatory markers were raised (WBC 14 X10^9/L, CRP 346 mg/L, procalcitonin 3.7 µg/L). Blood cultures demonstrated no growth. X-rays taken of his left tibia and fibula showed no soft tissue gas lucency or osteomyelitis. Referral

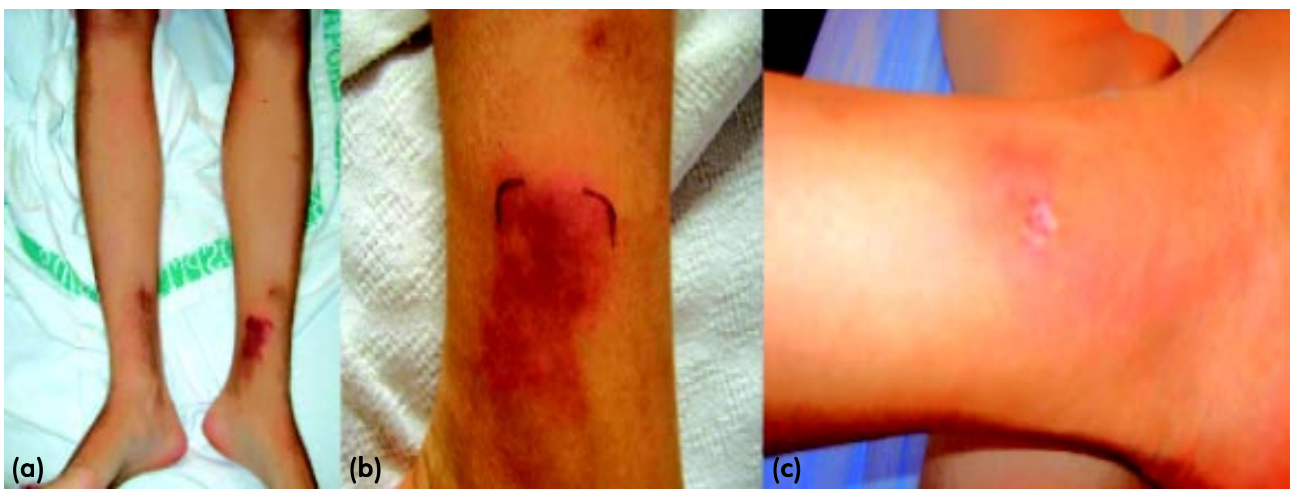

Figure 2. (a) Erythematous plaque above left medial malleolus at presentation. (b) Close up view. (c) Resolution two weeks after treatment (skin depression from biopsy).

to the orthopaedic department was made as there was concern of necrotizing fasciitis. The orthopaedic team suggested surgical exploration as necrotizing fasciitis was a possibility. The patient was reluctant to undergo surgical intervention, and the antibiotic treatment was switched from amoxicillin/clavulanate to penicillin, clindamycin and gentamicin.

A referral to the dermatology team was made on day four of admission, as the managing team was concerned over the poor response to antibiotic treatment. Clinically, this patient was alert and vital parameters were stable. There was extensive erythema and oedema over his left leg. There were large bullae and ecchymoses in well-defined areas (Figure 3a).

The dermatological diagnosis was bullous erysipelas.

While antibiotics were infused daily, strict local skin care was performed concurrently. This included potassium permanganate compresses, compression bandage and elevation of the affected leg. He was discharged after 2 weeks of in-hospital stay, and continued outpatient follow up. Significant improvement was seen (Figures 3b & 3c).

Discussion

Both erysipelas and cellulitis are manifested clinically by rapidly spreading areas of oedema, redness, and warmth, sometimes accompanied by lymphangitis and inflammation of the regional lymph nodes. The skin surface may resemble an orange peel (i.e. peau d'orange) due to superficial cutaneous oedema surrounding the hair follicles, which causes dimpling in the skin because they remain tethered to the underlying dermis. Vesicles, bullae, and cutaneous haemorrhage in the form of petechiae or ecchymoses may develop on the inflamed skin. Systemic manifestations are usually mild. Clues to potentially severe deep soft-tissue infection include the following: (1) pain disproportionate to the physical findings, (2) violaceous bullae, (3) cutaneous haemorrhage and necrolysis, (4) skin sloughing, (5) skin anaesthesia, (6) rapid progression, and (7) gas in the tissue.[4]

After eliciting a thorough history and performing a physical examination, there is usually a fairly limited need for further laboratory testing for routine cellulitis cases. A complete blood count with differential may be helpful. Patients with cellulitis usually have normal or slightly elevated leukocyte counts. Cultures of any bullae, pustules, or ulcers can be performed in any patient with

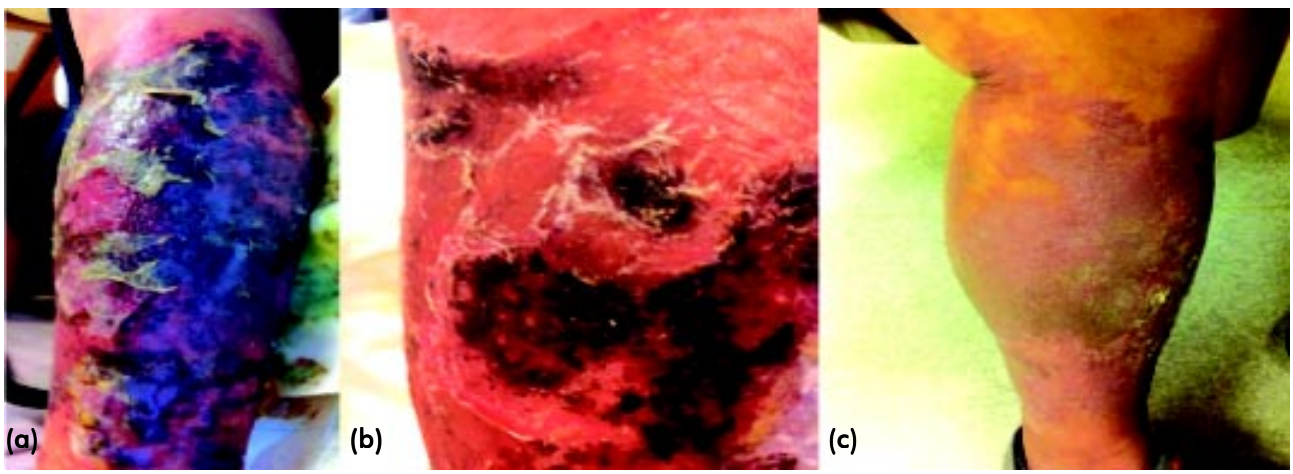

Figure 3. (a) Diffuse erythema, oedema and crusts over left leg at presentation. (b) Reduced erythema and oedema after four weeks. (c) Residual post inflammatory hyperpigmentation after eight weeks.

presumed cellulitis, as these cultures are relatively non-invasive and can provide informative results if positive. Needle aspiration or punch biopsy for culture are not recommended, as they are rarely informative.[5]

Because of their low yield, blood cultures are not fruitful for the typical case of erysipelas or cellulitis, unless it is particularly severe or in setting of immunocompromised patients.[6] Imaging can help to distinguish cellulitis from more severe infections. Plain-film radiography and magnetic resonance imaging (MRI) can be used to rule out accompanying osteomyelitis.[7] MRI or computed tomography can also help determine the extent of infection and help distinguish cellulitis from pyomyositis or necrotizing fasciitis.[8] Ultrasonography and MRI are helpful for determining any accumulations of pus and in guiding aspiration.[8] The lack of clinical response should alert us to consider infections from unusual organisms, resistant strains of staphylococcus or streptococcus, or deeper processes, such as necrotizing fasciitis. In patients who become increasingly ill, necrotizing fasciitis should be considered, with an aggressive evaluation, and antibiotic treatment modified, on the basis of Gram stain results, culture results, and antimicrobial susceptibilities of organisms obtained from surgical specimens. Cutaneous findings of necrotizing fasciitis include purple bullae, sloughing of skin, marked oedema, and most importantly systemic toxicity, which usually mandates prompt surgical intervention. The choice of antimicrobial is one that targets aerobic gram-positive and gram-negative bacteria.

Skin and soft tissue infections in immuno-compromised hosts (such as underlying diabetes mellitus, neutropenia and chronic renal failure) pose diagnostic challenges as infections are caused by diverse organisms (including organisms not ordinarily considered to be pathogens in otherwise healthy hosts); infection of the soft tissues may be part of a broader, systemic infection; and the degree and type of immune deficiency attenuate the clinical findings. Broad-spectrum empirical antimicrobials may be necessary.

The role of local skin care

Case 4

A 46-year-old Indian female, without significant medical history, was admitted for left leg swelling for three days. This was associated with severe pain and she was unable to ambulate. She had no fever and was well otherwise. Her inflammatory markers were raised (WBC 16.8 X10^9/L, CRP 288 mg/L, procalcitonin 0.77 µg/L). Blood cultures demonstrated no bacteraemia. X-ray taken of her left tibia and fibula showed diffuse soft tissue swelling. She was treated as for bullous erysipelas and was started on IV clindamycin and subsequently amoxicillin/clavulanate.

A referral to dermatology was made on day 2 of admission for advice to further management. Clinically, this patient was alert and vital parameters were stable. There was extensive erythema and oedema over her left leg. There were bullae of various sizes, some which were de-roofed on the ward (Figure 4a). The dermatological diagnosis was bullous erysipelas. Similar to case 3, local skin care was administered concurrently while she was on antibiotics. There was regular review by a wound nurse who advised on potassium permanganate compresses, compression bandage and elevation of the affected leg. Improvement was seen after 6 days (Figure 4b).

Discussion

Elevation of the affected area, an important and often neglected aspect of treatment, quickens improvement by promoting drainage of the oedema and inflammatory substances. Patients should also receive appropriate therapy for any underlying condition that may have predisposed to the infection, such as tinea pedis, venous eczema ("stasis dermatitis"), or trauma. Each attack of cellulitis causes lymphatic inflammation and

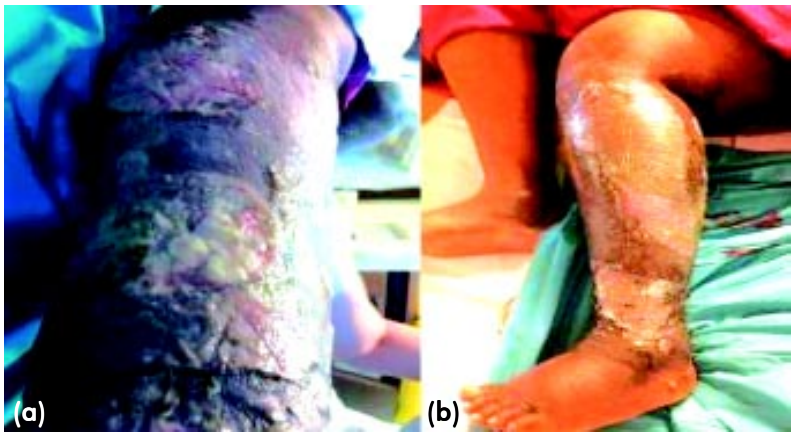

Figure 4. (a) Diffuse oedema and large bullae (de-roofed) with purulent base over left leg at presentation. (b) Reduced oedema and purulence after six days.

possibly some permanent damage. Severe or repeated episodes of cellulitis may lead to lymphoedema, sometimes substantial enough to cause elephantiasis. Measures to reduce recurrences of cellulitis include treating interdigital maceration, keeping the skin well-hydrated with emollients to avoid dryness and cracking, and reducing any underlying oedema by such methods as elevation of the extremity, compressive stockings or pneumatic pressure pumps, and, if appropriate, diuretic therapy.

Which antibiotic should we use?

In our first case, amoxicillin/clavulanate was initiated; second case had penicillin and cloxacillin; third case had amoxicillin/clavulanate which was switched to penicillin and clindamycin and gentamycin; and our fourth case had clindamycin which was switched to amoxicillin/clavulanate.

Discussion

The Department of Infectious Diseases in Singapore General Hospital has recently updated their antibiotic guidelines for cellulitis. For cases of cellulitis without background of diabetes mellitus, cefazolin 2 g 8 hourly is recommended as first-line treatment. Cefazolin (second generation cephalosporins) covers *Staphalococcus* and *Streptococcus* infections (the most common causes of cellulitis). It has a longer half-life than penicillin and cloxacillin thus requiring less frequent dosing. It is also less thrombophlebitic than penicillin and cloxacillin. For patients with penicillin allergy, vancomycin is recommended as an alternative. In most cases, the duration of treatment with antibiotics should not exceed seven days, and it is recommended to switch patients to oral antibiotics such as amoxicillin/clavulanate or clindamycin as early as deemed appropriate. Evidence suggests that treatment for more than 7 to 14 days is not necessary.[9] However, long courses of up to 2 weeks or more are commonly prescribed.[10] Exposing patients to unnecessarily prolonged therapy or treatment regimens with an unnecessarily broad spectrum of activity can increase incidence and severity of *Clostridium difficile* infection.

A recent publication suggests that implementation of a guideline for the management of in-patient cellulitis and cutaneous abscess led to shorter durations of more targeted antibiotic therapy and decreased use of resources without adversely affecting clinical outcomes.[11]

Routine cellulitis without underlying abscess formation is usually caused by *Streptococci*.[12] *Staphylococcus aureus* is a possible culprit in cases with underlying abscess formation or a history of penetrating trauma. Therapeutic options to cover *Streptococci* and Methicillin-sensitive

S. aureus include dicloxacillin, cephalexin, clindamycin, or erythromycin if resistant organisms are not prevalent in the community. Most patients can immediately receive oral treatment. In more severely affected patients or patients unable to tolerate oral therapy, intravenous therapy with a penicillinase-resistant penicillin such as cloxacillin, or a first-generation cephalosporin such as cefazolin, or, for patients with penicillin allergy, clindamycin or vancomycin can be used. Methicillin-resistant *S. aureus* (MRSA) infection should be considered in high-risk populations.[13]

In conclusion, in the clinical assessment, all efforts should be made to ensure an early accurate diagnosis with a good detailed history and physical examination, supplemented with the appropriate laboratory markers as necessary. Appropriate use of antibiotics in established cases of erysipelas and cellulitis, together with meticulous local skin care, will ensure early recovery of our patients.

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