Case Report

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STREPTOCOCCUS DYSGALACTIAE BACTEREMIA SECONDARY TO LEFT LOWER LIMB BULLOUS CELLULITIS PRECIPITATEDBY GOUT: CASE REPORT

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Abstract

A Chinese man of 55 years old was admitted to the hospital due to a fever and pain in his left lower limb manifesting as left metatarsal pain. His symptoms were accompanied by swelling, redness, tenderness, and the development of blisters. The patient had gout flare-up which contributed to the development of bullous cellulitis exacerbated by bacteremia. Report from blood culture revealed a positive aerobic culture of gram-positive cocci, *Streptococcus dysgalactiae*, sensitive to Penicillin and Ampicillin. The patient had a medical history of dyslipidemia, hypertension, and impaired glucose tolerance. His condition necessitated a multidisciplinary management and a replacement of antibiotic regimen despite receiving Ampicillin- Sulbactam (Unasyn) for initial treatment. This was due to the development of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome induced by Ampicillin-Sulbactam, among other complications. This case report describes the patient's presentation, diagnosis, and course of treatment.

Keywords: Bullous cellulitis, Streptococcus dysgalactiae, DRESS syndrome, Gout flare, Ampicillin-Sulbactam.

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Background

Bullous cellulitis is a severe form of cellulitis, an acute bacterial infection of the dermis and subcutaneous tissue. This condition is characterized by the presence of blisters in addition to the typical signs of cellulitis such as erythema, warmth, swelling, and pain. The infection typically begins with a breach in the skin barrier, such asa cut, abrasion, insect bite, or a pre-existing skin condition like eczema [6]. With the skin barrier compromised by gout-related inflammation, an opportunistic pathogencan invade the tissue. As the infection progresses, *Streptococcus dysgalactiae*, the causative pathogen in this case, invade deeper tissues and enter the bloodstream, leading to bacteremia. Bacteremia is marked by the presence of bacteria in the blood which can trigger systemic inflammatory responses [8].

Upon entry, the bacteria proliferate rapidly, releasing various virulence factors and toxins. These include enzymes like hyaluronidase and streptokinase, which break down connective tissue and facilitate bacterial spread. The immune system responds to the infection by activating white blood cells, particularly neutrophils, which migrate to the site of infection. These cells release inflammatory mediators such as cytokines and chemokines, leading to increased blood flow, erythema, warmth, and edema in the affected area [9].

The inflammatory response leads to increased vascular permeability, allowing fluid to accumulate between the epidermis and dermis, resulting in blister formation. The bullae in bullous cellulitis contain clear or sometimes serous fluid, which can become purulent if secondary infection occurs. The presence of bullae indicates a severe inflammatory response and significant tissue damage. The pathophysiology of bullous cellulitis exacerbated by bacteremia involves bacterial invasion, rapid proliferation, and the subsequent immune response, leading to local tissue damage and systemic complications if untreated [10]. The causative agent particularly adept at evading the immune system and spreading through tissues, making early and effective treatment crucial.

The development of complications like DRESS syndrome highlights the need for careful monitoring of patients

with multiple comorbidities. DRESS syndrome is a rare but lethal delayed drug hypersensitivity reaction. The clinical findings include drug-induced rash, eosinophilia in peripheral blood count, and systemic symptoms like fever, involvement of lymph nodes, and involvement of other solid organs such as liver, kidney, and lung. Antiepileptic medications are the most frequent cause; however, antibiotics and other medications are also linked to it [7].

Prompt diagnosis and appropriate treatment are essential for reducing complications and improving outcomes in individuals with bullous cellulitis and DRESS syndrome. Therapeutic management for bullous cellulitis often involves antibiotic therapy targeting the causative bacteria, which may require intravenous administration initially depending on the severity. Supportive measures such as elevation of the affected limb, wound care, and pain management are also crucial. In contrast, managing DRESS syndrome involves immediate cessation of the offending drug, supportive care for symptoms, and sometimes corticosteroids to suppress inflammation. Both conditions require close monitoring of clinical progression and may necessitate involvement of multiple medical specialties for comprehensive care.

By classifying the pathophysiological mechanisms underlying this complication and implementing evidence-based interventions, clinicians can improve patient outcomes and mitigate the burden of bullous cellulitis and DRESS syndrome related morbidity and mortality. This case report will concentrate on the management of gout and treatment of bullous cellulitis exacerbated by bacteremia.

Case Presentation

A 55-year-old male patient was admitted to the hospital with complaints of having a fever and pain in his left lower limb which initially presented as metatarsal pain. Over time, his symptoms progressed to include significant swelling, redness, tenderness, and blister formation, indicative of an acute inflammatory process. His medical history is significant for several chronic conditions. He has a history of hypertension, dyslipidemia, and recurrent gout, conditions that predispose him to a higher risk of infections and his initial therapy triggered DRESS syndrome. Hence, Unasyn was discontinued and his antibiotic regimen was replaced with Cloxacillin, then Benzylpenicillin which is more effective against Streptococcus dysgalactiae based on sensitivity test results.

Investigation

Table 01: Laboratory parameters

Criteria	Day1	Day 4	Day5	Day7	Day10	Day14	Day16	Day18
BP	164/ 89	140/ 72	163/ 77	142/ 78	130/ 83	147/ 84	152/ 89	161/ 96
Temp	37	38	38	37.7	37	37.3	37	37
HR	97	97	94	90	96	84	85	75
SpO_2	98	88	91	96	96	97	98	98
WBC	12.2	-	17.0	14.5	10.1	11.7	10.3	-
Plt	151	-	290	425	691	738	635	-
Hb	12.8	-	12.5	12.1	11.1	12.2	12.4	-
CRP	44.41	-	23.23	8.51	5.42	-	-	-
Cr	90.6	-	73.4	71.7	76.6	67.0	70.7	-
AST	30	-	56	113	79	63	39	-
ALT	48	-	72	143	164	198	152	-
DXT	7.9	8.1	8.9	7.3	5.8	5.8	5.3	5.9

The vital investigation revealed a spike in blood pressure on day 5 due to Ampicillin-Sulbactam (Unasyn) associated with inflammatory response from DRESS syndrome. On day 14 until day 18, infections were resolving but the body may still be under stress which temporarily elevate blood pressure. According to CPG for The Management of Hypertension, it complications. Additionally, he has impaired glucose tolerance, which can compromise immune responses and slow the healing process. His previous medical records also indicate peripheral vascular disease-like symptoms, which were managed with Simvastatin. This history of vascular issues is relevant as it can lead to poor circulation, particularly in

he lower extremities, making them more susceptible to infections such as cellulitis.

The patient also had a history of smoking, which he ceased 10 years ago, and regular alcohol consumption. He was initially treated with Ampicillin-Sulbactam (Unasyn) for the suspected bacterial infection. However, is recommended to consider pharmacotherapy if blood pressure consistently measures above 140/80 mmHg. The choice of first-line monotherapy options includes diuretics, ß-blockers, CCBs, ACEIs, and ARBs [2]. Temperature and oxygen saturation were normal throughout the patients' admission. The patient had elevated WBC and platelet and low level of hemoglobin throughout hospitalization due to the body's immune response to the bacteremia. They were associated with the severity of infection observed in bullous cellulitis. The patient also had elevated CRP levels on day 1 until day 5 which correlates with the inflammatory response due to acute gout flare. However, the CRP level decreased on day 7 indicates that the inflammation was resolving. Elevated ALT and AST commonly associated with alcohol consumption due to its hepatotoxic effects. The patient is a regular alcohol drinker. The patient also exhibited elevated fasting blood glucose levels from day 1 to day 5 indicating hyperglycemia. Subsequently, over the following days, his hyperglycemic state resolved.

Differential Diagnosis

Patient was diagnosed with bullous cellulitis exacerbated by bacteremia. Blood culture test was performed to identify the organism responsible for bacteraemia and the effective antibiotic regimen for the treatment. Results from blood culture test revealed gram-positive cocci, Streptococcus dysgalactiae, sensitive to Penicillin and Ampicillin. Patient also had DRESS syndrome due to the administration of Ampicillin-Sulbactam (Unasyn). Given the complexity of DRESS syndrome, prompt recognition and withdrawal of the offending drug are critical. Ampicillin-Sulbactam (Unasyn) was discontinued and replaced with Cloxacillin, then Benzylpenicillin.

Treatment

Patient underwent a complex treatment regimen for several medical conditions throughout his admission at the hospital. Patient initially prescribed Azithromycin 500 mg orally daily for bullous cellulitis on the day of admission then replaced with IV Ampicillin-Sulbactam based on blood culture sensitivity test results which revealed gram-positive cocci, Streptococcus dysgalactiae, sensitive to Penicillin and Ampicillin. IV Ampicillin-Sulbactam was administered at varying doses; 3g TDS on day 2 and 3g QID starting on day 4 for the same condition, but was discontinued due to suspected DRESS syndrome. Following the diagnosis of DRESS syndrome attributed to Ampicillin-Sulbactam, the antibiotic was replaced with IV Cloxacillin 3 MIU every 4 hours starting on day 7 for bullous cellulitis. This treatment was subsequently changed to IV Benzylpenicillin 3 MIU 6 times daily from day 12 until patient was discharged. Prednisolone was administered on day 11 at 20 mg OD, utilized for the treatment of DRESS syndrome.

The patient's regimen for acute gout flare management included Colchicine initiated with a tapering dose regimen of 0.6 mg TDS, then BD, and eventually OD starting on day 8 which remains ongoing. To address hypertension, IV Frusemide was prescribed at 40 mg TDS then adjusted to BD and OD on day 10, continuing as an ongoing therapy. Amlodipine 5 mg OD and Losartan Potassium 50 mg OD also had been administered for hypertension. Empagliflozin was initiated at 12.5 mg OD for impaired glucose tolerance but discontinued shortly after starting and replaced with Insulin Actrapid 6.0 IU TDS. Diclofenac Sodium 50 mg TDS was prescribed briefly for pain and inflammation management associated with gout flares before being stopped. To manage severe inflammation, IV Tramadol Hydrochloride was introduced at 50 mg TDS but was discontinued after a short course. It was then replaced with IV Hydrocortisone Sodium on day 10 at 100 mg OD, adjusted to TDS on day 12 and BD on day 13, continuing as an ongoing treatment.

Throughout the hospitalization, the patient also received ongoing treatments for chronic conditions including Simvastatin 20 mg OD for dyslipidemia, topical therapy like Potassium Permanganate solution twice daily for wound care and Miconazole Nitrate 2% Cream 1 g BD to prevent secondary fungal infections. IV Enoxaparin Sodium 40 mg OD was initiated for prophylaxis against deep vein thrombosis while Chlorpheniramine Maleate 4 mg OD for allergic reactions. This comprehensive treatment approach aimed to manage multiple concurrent medical issues, adjusting therapies as necessary based on the patient's response and evolving clinical condition.

Discussion

The patient reported left lower limb swelling persisting for four days, accompanied by redness, tenderness, and later developing blisters. Despite these symptoms, he retained ambulatory function although at a slower pace. The swelling coexists with a four-day history of fever, suggestive of an infectious etiology related to the observed bullous cellulitis of the left lower limb. Given his history of recurrent podagra and elevated uric acid levels, the cellulitis was likely secondary to gout exacerbation, underscoring the importance of managing both the infectious component and underlying metabolic conditions.

Furthermore, the patient also reported occasional frothy urine, polyuria, and polydipsia, indicating renal involvement and in need of additional evaluation to assess renal function and exclude underlying renal pathology. On the day of admission, the patient vital signs indicated stable oxygenation but highlighted concerns of hypertension and tachycardia with a normal body temperature of 37°C, elevated blood pressure of 164/89 mmHg, increased heart rate of 104 bpm, normal respiratory rate of 20 bpm, and oxygen saturation of 98%.

These findings necessitated close monitoring and potential intervention to address cardiovascular health, aiming to mitigate risks associated with elevated blood pressure and heart rate.

According to National Antimicrobial Guideline (NAG) 2019 by Ministry of Health Malaysia, the treatment for cellulitis of skin and soft tissue infections preferred to be Cloxacillin

200mg/kg/day IV in 4 divided doses with maximum dose of 12gm/day for 5-7 days. The alternative medication for this would be Amoxicillin 25-50mg/kg/day orally in 3 doses for 7 days or Cephalexin 25-50mg/kg/day orally in divided doses for 5-7days. Medicine needs to be administered using parenteral route for extensive lesions. Total treatment until 3 days after acute inflammation disappears [3]. The patient initially prescribed Azithromycin 500 mg orally daily for bullous cellulitis upon admission then replaced with IV Ampicillin-Sulbactam based on blood culture results which revealed gram-positive cocci, Streptococcus dysgalactiae, sensitive to Penicillin and Ampicillin. However, Ampicillin-Sulbactam triggered DRESS syndrome, thus, his antibiotic regimen was replaced with IV Cloxacillin 3 MIU every 4 hours daily. This treatment was later replaced with IV Benzylpenicillin 3 MIU 6 times daily since it is more effective to combat Streptococcus dysgalactiae bacteremia.

To treat DRESS syndrome, the patient was prescribed with Prednisolone. The management of DRESS syndrome varies based on the severity ranging from mild cases to severe cases with viral reactivation [5]. Mild cases are characterized by the absence of severe signs, initial management typically involves discontinuing the suspected culprit drug and employing supportive measures. Topical corticosteroids can be applied to alleviate skin manifestations, while emollients soothe dry, irritated skin. Antihistamines are administered to mitigate itching and other allergic symptoms, providing relief without the need for systemic intervention unless symptoms worsen. Moderate cases of DRESS syndrome exhibit signs such as significantly elevated transaminases, kidney failure, lung disease, hemophagocytosis, or cardiac abnormalities. These indicators warrant systemic treatment with corticosteroids, typically Prednisolone at a dosage of 1 mg/kg per day. This approach aims to suppress the immune response and mitigate systemic inflammation, addressing both cutaneous and visceral manifestations of the syndrome.

In severe cases where patients present with life-threatening signs such as hemophagocytosis, spinal cord or encephalitis, liver failure, or respiratory failure, more aggressive management strategies are necessary. Treatment involves high-dose corticosteroids along with therapy. IVIG is administered at a dosage of 2 g/kg per day for five days, aiming to modulate the immune response and attenuate systemic inflammation. This combined approach is crucial in stabilizing patients and preventing further deterioration of organ function. For severe cases complicated by viral reactivation, additional measures are implemented to address the viral [11]

component contributing to the syndrome. Alongside corticosteroids and IVIG, antiviral therapy such as Ganciclovir is initiated to suppress viral replication and reduce associated complications. This comprehensive therapeutic approach addresses both the inflammatory and infectious aspects of DRESS syndrome, aiming to achieve rapid resolution of symptoms and prevent long-term sequel. The patient continued to recover from bullous cellulitis secondary to bacteremia and DRESS syndrome with significant improvement in skin rash and overall clinical symptoms by the time he discharged.

During hospitalization, the patient's clinical condition remained complex with dual management of cellulitis and concurrent gout flare. After 2 weeks at the hospital, the patient showed signs of volume overload with a new systolic murmur suggestive of infective endocarditis and an acute gout flare. He was prescribed with Colchicine with a tapering dose regimen of 0.6 mg TDS, then BD, and eventually OD which remains ongoing to decrease the frequency and intensity of pain from his gout flare.

According to the Malaysia CPG for Gout, the first-line therapy for managing urate levels is Allopurinol. Initially, it is recommended to start at a dose of 100 mg per day, with adjustments made in increments of 100 mg every 2-4 weeks based on SU concentration until the target level is achieved. For maintenance therapy, doses of at least 300 mg per day are typically required to reach the desired SU target, with a maximum recommended dose of 900 mg per day. Allopurinol can be administered once daily as a single dose or divided into 2 or 3 doses daily if exceeding 300 mg per day [1].

In the management of acute gout flares and flare prophylaxis, Colchicine is recommended. For treating gout flares, an initial dose of 1 mg is advised, followed by 0.5 mg one hour later. Further tablets should not be taken for at least 12 hours, after which treatment can resume if necessary. The maximum dosage during a flare is 0.5 mg every 8 hours until symptoms are relieved. After completing a course of treatment for a flare, another course should not be initiated for at least 3 days. For flare prophylaxis, Colchicine is prescribed at a daily dose of 0.5 mg once or twice daily. If a flare is anticipated, a higher initial dose of 1 mg may be taken at the first sign, followed by 0.5 mg one hour later. Subsequently, the prophylactic dose should resume after a 12-hour interval. These guidelines aim to optimize the management of gout by effectively lowering urate levels and managing acute flares while minimizing the risk of recurrence and complications associated with the condition.

Outcome and Follow-Up

The patient condition required a comprehensive, multidisciplinary approach to manage the complex

interplay of his bullous cellulitis, underlying comorbidities, and treatment complications. Initially, his symptoms of fever, pain, and significant swelling in the

left lower limb, compounded by the presence of bullae, were managed with broad-spectrum antibiotics. With the adjusted antibiotic therapy, the patient began to show signs of clinical improvement. The inflammation and pain in his left lower limb gradually subsided and the bullae started to heal. His fever resolved, indicating a positive response to the targeted antibiotic treatment.

Follow-up plans included regular consultations with rheumatology and dermatology specialists to manage his gout and skin complications. Ongoing monitoring of his inflammatory markers and blood counts was necessary to ensure a sustained recovery and to detect any potential relapses or complications. Regular monitoring of his renal and liver function tests was crucial due to the potential side effects of long-term antibiotic use and his existing comorbidities.

Conclusion

This clinical case underscores the complexities involved in managing severe infections in patients with multiple comorbidities. The presentation of bullous cellulitis on this patient was further complicated by the identification of Streptococcus dysgalactiae as the causative pathogen and the subsequent development of DRESS syndrome. Early and accurate diagnosis was critical in managing the patient's condition. The initial presentation of erythema, edema, tenderness, and bullae in the left lower limb, coupled with systemic symptoms like fever, necessitated prompt medical intervention. Laboratory investigations, including blood cultures, were pivotal in identifying the specific pathogen responsible for the infection. This enabled the healthcare team to tailor the antibiotic regimen effectively, transitioning from broad-spectrum antibiotics to more targeted therapy was crucial in controlling the bacterial infection.

The effective management of the patient's comorbidities required a multidisciplinary approach involving specialists from various fields, including infectious disease, dermatology, rheumatology, and primary care. Each specialist played a vital role in addressing different aspects of his health, ensuring comprehensive care. The rheumatologists and dermatologists provided essential insights into managing his gout and skin complications, while the infectious disease specialists guided the appropriate antibiotic therapy. This collaborative approach was instrumental in managing not only the acute infection but also the chronic conditions and complications that arose during his treatment.

Finally, the fact that the patient's bullous cellulitis and its complications were successfully managed highlights the value of a multidisciplinary, patient-centered approach in the treatment of complex medical cases. The case illustrates how patients with severe infections and numerous comorbidities can benefit from early and accurate diagnosis, focused therapy, all-encompassing supportive care, and close observation.

Abbreviations

ALT: Alanine aminotransferase AST: Aspartate aminotransferase Cr: Creatinine
CRP: C-reactive protein DXT: Fasting blood glucose BP: Blood pressure
HR: Heart rate
SpO2: Oxygen saturation Temp: Temperature
Hb: Hemoglobin Plt: Platelets
WBC: White blood cell count MIU: Million international units IV: Intravenous
IVIG: Intravenous immunoglobulin OD: Omni die (every day)
BD: Bis in die (twice daily)
TDS: Ter die sumendum (three times daily) QID: Quarter in die (four times daily)
ACEi: Angiotensin-converting enzyme inhibitors ARB: Angiotensin II receptor blockers
CCB: Calcium channel blockers CPG: Clinical Practice Guideline
DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

Conflict of Interest

Authors do not have any conflicts of interest.

Author Contributions

All Authors Contributed Equally.

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