CASE REPORT

Serum sickness-like reaction after the treatment of cellulitis with amoxicillin/clavulanate

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SUMMARY

Serum sickness-like reaction is a rare disease presentation. We describe a case of a man aged 58 years who presented with acute-onset polyarthralgia, intense pruritus of hands and feet, fever to 39.5°C and leucocytosis to $17.2 \times 10^3/\text{mm}^3$ 5 days after completing a 10-day course of amoxicillin/clavulanate for the treatment of finger cellulitis. With history, symptoms, physical examination findings and reported cases in the literature of serum sickness-like reactions to amoxicillin, a clinical diagnosis of serum sickness-like reaction was made. The patient was treated with non-steroidal anti-inflammatories with improvement in symptoms by the time of discharge.

BACKGROUND

Serum sickness-like reaction is a rare disease presentation. Amoxicillin/clavulanate is a widely used antibiotic. This clinical case depicts a rare side effect associated with amoxicillin/clavulanate. Serum sickness-like reaction is a diagnosis of exclusion, requiring a detailed history and laboratory work-up.

CASE PRESENTATION

We report the case of a man aged 58 years with a medical history notable only for remote left anterior cruciate ligament repair who was admitted for the work-up of acute-onset polyarthralgia, intense pruritus of hands and feet and fever for 4 days.

The patient reported having been bitten on the tip of the third finger of his right hand while steaming blue crabs. Initially, he applied Epsom salts to the wound. However, 2 days later, the wound, initially red in coloration, had transitioned to purple and finally black while also enlarging in size with accompanying pain. At that time, it involved only the portion of his finger distal to the distal interphalangeal joint. Because of the progressive changes in his finger, he presented to a local urgent care facility and was diagnosed with cellulitis. He was prescribed and completed a 10-day course of amoxicillin/clavulanic 875 mg twice a day, noting complete resolution of his finger symptoms within the first 4 days of treatment.

Five days following completion of his antibiotic course, the patient endorsed acute-onset swelling of the dorsum of his right hand along with pain and swelling of his right second and third metacarpophalangeal (MCP) joints. These signs were associated with stiffness of the right hand along with subjective fevers and chills and malaise. He presented to a local emergency department.

Laboratories were notable for a leucocytosis to $14 \times 10^3/\text{mm}^3$ ($4.5\text{--}11 \times 10^3/\text{mm}^3$) without left shift, aspartate transaminase 73 U/L (0–31 U/L), alanine transaminase 84 U/L (0–31 U/L), erythrocyte sedimentation rate 43 mm/hour (4–30 mm/hour), C reactive protein 16.9 mg/dL (<0.5 mg/dL), uric acid 3.8 mg/dL (3.5–7.2 mg/dL), and negative rheumatoid factor, hepatitis B surface Ag and Lyme EIA. He was admitted to the hospital and treated with intravenous vancomycin and ciprofloxacin overnight. The following morning, these antibiotics were discontinued, and he was given a diagnosis of gout and advised to follow up with rheumatology as an outpatient.

The patient continued to experience pain in his right hand and subjective fevers and chills. He also developed new pain, swelling and stiffness in his right shoulder, left wrist, left hand, left shoulder and left knee along with intense pruritus of both hands and feet. This prompted him to present to the emergency department at our hospital.

In the emergency department, the patient was febrile (39.5°C), tachycardic (102 bpm) and hypertensive to 170/100 mm Hg. Blood cultures were sent, and he was started on doxycycline, piperacillin/tazobactam and vancomycin.

On physical examination, several MCP joints were moderately boggy, but none were erythematous or tender. Active movement did not elicit pain, and the patient had 5/5 grip strength bilaterally. There was modest tenderness over the heads of both biceps tendons, but no detectable shoulder effusions. Elbow and wrist effusions were similarly not detected. His cardiovascular, respiratory, abdominal and neurological examinations were unremarkable.

INVESTIGATIONS

The patient's complete blood count showed a white cell count (WCC) of $17.2 \times 10^3/\text{mm}^3$ ($4.5\text{--}11 \times 10^3/\text{mm}^3$) with neutrophil predominance, haemoglobin level of 14.2 g/L (12–15 g/L) and platelet count of 246 000/ μL (150 000–350 000/ μL). Liver enzymes and renal function tests were within normal limits. Erythrocyte sedimentation rate was 53 mm/hour (4–30 mm/hour), C reactive protein was 14.1 mg/dL (<0.5 mg/dL), C3 was 100 mg/dL (79–152 mg/dL), C4 was 20 mg/dL (12–42 mg/dL) and total complement activity (CH50) was 51 U/mL (31–60 U/mL). Urinalysis was notable for trace proteinuria, and there was no haematuria. Gonorrhoea and chlamydia nucleic acid testing was negative, blood cultures were negative, serologies for antistreptolysin, HIV, hepatitis

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C, hepatitis B core, Lyme, mycoplasma, syphilis and parvovirus B19 were negative. Serologies for rheumatoid factor, cyclic citrullinated peptide, HLA-B27 and antinuclear antibody were negative.

Arthrocentesis of the left knee showed 3689 WCC/mm³ (72% PMN) with negative gram stain and no crystals. Radiographs of bilateral hands and wrists were notable only for degenerative osteophytes and sequelae of trauma in the left hand. Transthoracic echocardiogram demonstrated grade I diastolic dysfunction.

DIFFERENTIAL DIAGNOSIS

- ▶ Septic arthritis
- ▶ Reactive arthritis
- ▶ Rheumatoid arthritis
- ▶ Systemic rheumatic disease
- ▶ Viral arthritis
- ▶ Lyme disease
- ▶ Subacute endocarditis
- ▶ Rheumatic fever
- ▶ Gout
- ▶ Pseudogout
- ▶ Serum sickness-like reaction

TREATMENT

The patient was admitted to Internal medicine service and continued on doxycycline and piperacillin/tazobactam. Infectious Diseases and Rheumatology services were consulted. Several features of his history argued for serum sickness as the diagnosis, including his fever, polyarthralgia and the intense pruritus of his hands and feet. The time course was also thought to be consistent, in that this diagnosis typically arises 1–2 weeks after exposure to the culprit agent, which, in this case, was thought to be amoxicillin/clavulanate. Consequently, antibiotics were discontinued, and symptomatic treatment with non-steroidal anti-inflammatories was recommended.

OUTCOME AND FOLLOW-UP

Three days after admission, the patient reported dramatic improvement in pain and range of motion. Examination was notable for minimal residual swelling and full range of motion in all but the right wrist. The patient was discharged home with follow-up with his primary care physician.

DISCUSSION

We describe the case of a patient developing fever, polyarthralgia, intense pruritus of hands and feet and leucocytosis 5 days after completing a 10-day course of amoxicillin/clavulanate to treat cellulitis.

Aetiologies of fevers, polyarthritis and leucocytosis include septic arthritis, reactive arthritis, viral arthritis, rheumatoid arthritis, systemic rheumatic diseases, Lyme disease, subacute endocarditis, rheumatic fever, gout, pseudogout and serum sickness-like reaction. At first glance, the patient's presentation was concerning for septic arthritis. Indeed, the patient noted subjective improvement following administration of intravenous antibiotics. However, his physical examination was not suggestive of septic arthritis, given septic arthritis is typically monoarticular.¹ Aspiration of the patient's left knee revealed 3689 WCC/mm³ with negative gram stain and negative culture growth. Bacterial joint infections typically have much higher cell counts: 50 000–150 000 cells/mm³.² Of course, the patient did receive antibiotics, but discontinuation of antibiotics did not worsen the

patient's condition. All above data, especially the involvement of multiple joints, argued against septic arthritis.

The patient reported no recent gastrointestinal or genitourinary symptoms with negative gonorrhoea and chlamydia nucleic acid testing, arguing against reactive arthritis. Viral arthritis as an aetiology for the patient's presentation was considered. Viral arthritis is commonly implicated with the following viral infections: parvovirus, hepatitis B, hepatitis C, Epstein-Barr virus (EBV) and rubella.³ On physical examination, the patient did not have the classic rubella rash, nor a facial rash (parvovirus) or cervical lymphadenopathy, suggestive of an EBV infection. Serologies for HIV, hepatitis B, hepatitis C and parvovirus B19 were negative. All above data argued against viral arthritis as an aetiology.

The patient reported no family history of autoimmune disorders, and his rheumatological work-up was negative (serologies for rheumatoid factor, cyclic citrullinated peptide, HLA-B27 and antinuclear antibody were negative), ruling against rheumatoid arthritis or other systemic rheumatic diseases as an aetiology. Although the patient lives in a Lyme endemic area, he denied any recent tick bites and Lyme serology was negative. Transthoracic echocardiogram demonstrated normal valve structure and function. Rheumatic fever can also present with a migratory polyarthritis. Although typically seen in the paediatric age group following streptococcal pharyngitis, there have been several case reports of rheumatic fever developing, following skin and soft tissue infections.⁴ The patient did meet the Jones diagnostic criteria with one major (arthritis) and three minor manifestations (arthralgia, fever and elevated ESR and CRP).⁵ Confirmatory anti-streptolysin was negative arguing against this aetiology.

His uric acid level was within normal limits at 3.8 mg/dL. Arthrocentesis of the left knee revealed no crystals. Radiographs of bilateral hands and wrists were notable only for degenerative osteophytes and sequelae of trauma in the left hand, rendering gout and pseudogout unlikely.

Given the patient's symptoms of fever, polyarthralgia and intense pruritus of his hands and feet; a consistent time course with signs and symptoms arising within 1 week following discontinuation of the culprit agent; and negative work-up for alternative diagnoses, a diagnosis of serum sickness-like reaction to amoxicillin/clavulanate was made.

Serum sickness-like reaction is a clinical diagnosis based on the onset of compatible signs and symptoms: fever, polyarthralgia, myalgia and rash 1–2 weeks after exposure to a culprit agent with resolution of the signs and symptoms following discontinuation of the offending agent. Other than a lack of rash, our patient's presentation fit nicely with a diagnosis of serum sickness-like reaction. Laboratory testing is important to rule out other potential diagnoses, given the lack of definitive confirmatory tests.⁶ Prior to treatment for cellulitis, our patient was not taking any medications, thus identifying amoxicillin/clavulanate as the offending agent.

Serum sickness-like reaction is clinically similar to serum sickness, but the pathophysiology is different.⁷ Serum sickness is a type III hypersensitivity reaction with deposition of immune complexes in tissues triggering an inflammatory response.⁸ The pathogenesis of serum sickness-like reaction is poorly understood, but is not thought to be mediated by immune complex deposition. One hypothesis that has been proposed for the pathogenesis of serum sickness-like reaction is an inflammatory response to drug metabolites.⁹

Amoxicillin/clavulanate is a combination antibiotic. It is composed of amoxicillin, a β -lactam antibiotic and clavulanate, a β -lactamase inhibitor.¹⁰ This combination increases the

antibiotic's spectrum of activity by restoring efficacy against β -lactamase-producing bacteria.¹⁰ It is widely used throughout the world to treat or prevent many infections, including sinusitis, otitis, pneumonia, bronchitis, urinary tract infections and in the case of our patient, cellulitis.¹⁰ Indeed, it is considered an essential medicine in a basic health system by the WHO.¹¹ Exposure to amoxicillin has been associated with delayed hypersensitivity, presenting similar to serum sickness with urticaria, angioedema, arthritis and arthralgia.¹²

Management of serum sickness-like reaction is two-pronged.¹³ One, discontinuation of the culprit agent. If discontinuation of the culprit agent is not possible, plasmapheresis has been employed to remove the culprit agent.¹⁴ Two, symptomatic treatment. Symptomatic treatment can be achieved by a stepwise approach. First, as in our patient's presentation, non-steroidal anti-inflammatories may be employed. If symptoms are not controlled or if more severe than our patient's presentation, namely high fevers and extensive rashes, a short course of glucocorticoids may be employed.¹⁵ Symptoms of serum sickness-like reaction typically resolve within 1–2 weeks of discontinuation of the culprit agent. To prevent recurrence, it is recommended that the culprit agent be avoided in the future. The question of whether related drugs, especially important in our patient's presentation, given that his reaction was thought to be secondary to a β -lactam antibiotic (amoxicillin), should also be avoided is controversial.

Learning points

- ▶ Symptoms of serum sickness-like reaction include: rash, fever, malaise and polyarthralgia or polyarthritis, occurring 1–2 weeks after exposure to a culprit agent.
- ▶ Serum sickness-like reaction is a clinical diagnosis made after a detailed history and laboratory work-up has excluded other diagnoses.
- ▶ Amoxicillin/clavulanate can cause a serum sickness-like reaction.
- ▶ Management of serum sickness-like reactions involves discontinuation of the culprit agent and symptomatic control with non-steroidal anti-inflammatories or glucocorticoids.
- ▶ To prevent recurrences, the culprit agent should be avoided in the future.

Contributors JP-F examined the patient, analysed the data and wrote the manuscript. CMH examined the patient and analysed the data. AN-A examined the patient, analysed the data and treated the patient. MM examined the patient and analysed the data. All authors approved the final version of the manuscript.

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