Streptokinase Induced Serum Sickness: A Case Report

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Statement of Contribution

The authors collectively contributed to this project with distinct roles and expertise. Bibek Shrestha played a central role in the conceptualization, data curation, formal analysis, methodology, project administration, original writing, review, editing, and visualization. Pradeep Shrestha provided resources, supervision, validation, conceptualization, investigations, and data curation. Rebecca Pradhan and Sudip Bastakoti both contributed to supervision, validation, and investigations. Each author's contribution was integral to the project's success, ensuring the accuracy and reliability of the findings presented in this work.

S. N	Name	Contribution
1	Bibek Shrestha	Conceptualization, data curation, formal analysis, methodology, project administration, original
2	Pradeep Shrestha	Resources, supervision, validation, conceptualization, investigations, and data curation
3	Rebicca Pradhan	Supervision, validation, and investigations.
4	Sudip Bastakoti	Supervision, validation, and investigations.

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ABSTRACT

Serum sickness is a Type III immune complex mediated hypersensitivity reaction which is characterized by fever, rashes, arthralgia and haematuria which occurs within 2 weeks of exposure of the offending agent. Medications including streptokinase are one of the rare and significant causes of Serum sickness due to presence of non-homologous protein. Streptokinase is used as a thrombolytic condition in different heart diseases including mitral valve stenosis. Although the condition is self-limiting, severe cases require intervention including NSAIDS, Steroids and Plasmapheresis. A 36-year-old female presented with the fever, arthralgia, shortness of breath after receiving thrombolytic treatment of streptokinase 3 days back for prosthetic valve thrombosis. Laboratory findings included increased ESR and CRP levels indicative of inflammatory disease, however all other rheumatological markers were negative. Based on the clinical history and investigations, Serum Sickness secondary to streptokinase was made. The condition was managed with supportive care, leading to resolution of the symptoms spontaneously. This case report highlights the importance of early recognition and management of serum sickness. Though serum sickness is a rare but is a significant complication of streptokinase therapy. Early diagnosis and appropriate management can prevent the severe outcome of the patient. Clinician should be vigilant for any thrombolytic complication during the treatment course.

Key clinical message

Serum sickness is rare; however, there is a significant hypersensitivity reaction to streptokinase used in different cardiac problems. Treatment often involves discontinuing the offending agent and administering corticosteroids, which can lead to complete recovery. This case underscores the complexities of managing prosthetic valve thrombosis and highlights the importance of monitoring and addressing potential complications of thrombolytic therapy.

Key words

Mitral valve stenosis; Serum Sickness; Streptokinase.

Introduction

Streptokinase is a widely used fibrinolytic agent for treating cardiovascular diseases, particularly in developing countries due to its cost-effectiveness[1]. Isolated from hemolytic streptococci, Streptokinase forms complexes with plasminogen to activate it into plasmin, which then dissolves blood clots and helps in improving reperfusion and left ventricular function in different cardiovascular diseases[2]. Being derived from bacterial protein, it can result in allergic reactions and bleeding, which are common adverse events. Patients might also have bradycardia and hypotension, along with fever, shivering, and rashes, as well as anaphylactic reactions[3]. Few case reports have reported serum sickness as a complication of Streptokinase therapy. Alexopoulos et al. (1984) have reported serum sickness as a complication of intravenous streptokinase when used for acute myocardial infaraction[4]. Serum Sickness is a Type III immune complex mediated hypersensitivity reaction which was first recognized in a patient who received heterologous antisera in the early 1990s. The symptoms usually occur after 1 to 2 weeks after exposure to offending agents and is a self-limited disease[5]. Although the condition is self-limiting, severe cases may require intervention. Treatment often involves discontinuing the offending agent and administering corticosteroids, which can lead to complete recovery[6]. In this we report a rare case from Tertiary Teaching Hospital of a 36-year-old female, with a known history of mitral valve stenosis secondary to Rheumatic Heart Disease who underwent Streptokinase treatment and presenting with Serum Sickness. This case underscores the complexities of managing prosthetic valve thrombosis and highlights the importance of monitoring and addressing potential complication of thrombolytic therapy.

Case History/ Examination

A 36-year-old female, with a known history of mitral valve stenosis secondary to rheumatic heart disease, underwent thrombolysis with streptokinase three months ago and presented with the primary complaints of shortness of breath on exertion for four days, orthopnea and paroxysmal nocturnal dyspnea (PND). She had a significant past medical history of mitral valve stenosis for which mitral valvotomy, double valve repair and redo mitral valve repair was done. Patients had recurring symptoms for which thrombolysis by streptokinase started 2 weeks ago. Following streptokinase treatment, the patient now presents with shortness of breath, fever, and bilateral knee pain for the past three days, with no history of photosensitivity, skin rashes, myalgia, malaise and lymphadenopathy. (Figure 1) Her bowel and bladder habits were normal. On examination, the patient was afebrile, pulse was 70/minute regular, respiratory rate was 20/minute, blood pressure was 100/70 mmHg. General examination revealed no pallor, icterus, cyanosis, edema and increased jugular venous pressure. Dermatological, cardiovascular and respiratory system examination was done and found to be normal. On the joint examination, there was no swelling, redness, or warmth on the knee joint.

Methods

Blood investigation was done and revealed Hemoglobin 9.65 gm% [Normal: 12-16 gm%], Neutrophil 41% [Normal: 40-60%], Lymphocyte 43% [Normal: 20-40%], Platelet 4,45,6000 cells/cum [Normal: 150,000-450,000 cells/cumm]. Her PT count was 32.8 second [Normal: 11-13.5 seconds], and INR was 2.5 [Normal: 0.8-1.2]. Her biochemical profile revealed Blood Urea Nitrogen to be 11 mg/dl [Normal: 7-20 mg/dl], Creatinine 0.7 mg/dl [Normal: 0.6-1.2 mg/dl], Sodium 137 mmol/L [Normal: 135-145 mmol/L] and potassium 3.7 mmol/L [Normal: 3.5-5.0 mmol/L]. Blood culture and urine culture were sterile. However, Hematology and serology tests suggested increased ESR and positive CRP Latex. The Renal function test was also normal. Further, Urinalysis was done and was found to be normal. (Table 1) Based on the history, examination, and investigations, serum sickness, hepatitis, and viral illness, including dengue, acute rheumatic fever, and subacute bacterial endocarditis, were considered for differential diagnosis. For further confirmation and to rule out other conditions, Hepatitis B antigen serology, antinuclear antibody, ELISA, Direct Coombs, Rheumatic factor, Anti CCP, and LDH tests were done to rule out other conditions and came negative. The absence of fever, thrombocytopenia, malaise, and weakness ruled out another differential diagnosis except for serum sickness and infective endocarditis. Having temporal association with streptokinase, absence of infective endocarditis symptoms (petechiae, Osler node, Janeway node, splinter haemorrhage, sign of sepsis), sterile blood culture, normal cardiac examination (including inspection, palpation, percussion and auscultation) , Serum sickness as a diagnosis was made. Further Rheumatological consultation was done, and a clinical diagnosis of serum sickness secondary to streptokinase therapy was made, considering the clinical history and laboratory investigation.

Conclusion and results

Supportive care involved continuous monitoring of thrombolysis related complications and symptomatic treatment for heart failure, including potential diuretics and oxygen therapy. For serum sickness as a complication of streptokinase therapy, pain management and steroid were considered which resolved spontaneously after 3 days of symptoms. The symptoms of serum sickness had resided so further, complement testing which include C3 and C4 for diagnosis was not sent. Echocardiography was done which suggested a high-pressure gradient prosthetic mitral valve of 11 mm Hg and diagnosis of a stuck mitral valve was made for which streptokinase thrombolysis was started. Though streptokinase was started again, the patient had developed a headache for which Neurology consultation was done, however haven't developed joint pain, fever and rashes. Post surgery echocardiography suggested a normal prosthetic valve with 4.4 mm hg mean gradient across the valve and normal left ventricular systolic function. The patient was ambulatory, tolerating oral feeds and stable. The patient was discharged after 18 days of hospital stay and given Oral Furosemide 40 mg BD, Oral Warfarin 9 mg OD, Oral Metoprolol 37.5 mg OD and Oral Aspirin 75 mg OD. On regular follow up, the patient was normal, and her shortness of breath has also resolved. Following streptokinase, she hasn't developed symptoms consistent with serum sickness like the previous one.

Discussion

Serum sickness is a delayed immune reaction characterized by fever, rash, arthralgias, lymphadenopathy, and polyarthritis. This condition is type III hypersensitivity reaction, caused by deposition of immune complexes[8]. The main etiology behind this is immune complex formation between human protein and non-human (heterologous) protein. Medications which consist of heterologous antigen as a component are the most common cause of it[9]. Streptokinase used as a thrombolytic agent has Serum Sickness which is a rare but significant side effect where patients present with mild to severe symptoms causing significant morbidity. Serum sickness can occur regardless of the dose or route of streptokinase administration, including intracoronary therapy[5]. Mohsenzadeh et al. (2020) found serum sickness to be prevalent in the Iranian

population due to antibiotic use, especially penicillin and the cephalosporin group of drugs[13]. Streptokinase has been used in various cardiovascular problems including myocardial infarction, arrhythmia and valve stenosis[7]. Few studies have shown an association between serum sickness and streptokinase therapy in the 20th century. This is the first study to show the association in the 21st century. In this case, we present a 36-year-old female who had a significant history of mitral stenosis and underwent thrombolysis by streptokinase treatment presented with the complaints of fever and arthralgia for 3 days. The correlation between detailed history and examination is required for suspected serum sickness. For the diagnosis, exposure of the offending agent within two weeks should be there, however in case of repeat exposure, within the few days before the presentation. The physical findings include arthralgia in the hands, feet, ankles, knees, and shoulders[5]. Rashes can also be present, which can be urticarial, maculopapular, or vasculitis eruption. The rashes might take weeks to resolve when the offending agent is resolved. Less commonly, there can be associated edema, lymphadenopathy, headache, and splenomegaly[13]. Our case presented with a history of streptokinase therapy within 2 weeks and presented with fever, arthralgia of bilateral knee joints. To assess potential additional etiologies and multi-organ system involvement, the clinician ought to consider the subsequent laboratory tests: erythrocyte sedimentation rate, C-reactive protein, total hemolytic complement, C3, C4, basic metabolic panel, liver transaminases, antinuclear antibody, rheumatoid factor, and complete blood count with differential[10]. These findings suggest the role of immune complexes in pathophysiology of serum sickness. In our case as well, the patient had elevated ESR and CRP level suggesting infectious pathology, however renal function test, and urinalysis were normal. To rule out other rheumatological conditions, antinuclear antibody, ELISA, Direct Coombs, Rheumatic factor, Anti CCP, LDH tests were done and were negative. Treatment typically involves withdrawal of streptokinase, but systemic corticosteroids may be necessary in severe cases with end-organ damage[11]. In this case, the patient had symptoms of fever and arthralgia for 3 days which relieved on withdrawing the offending agent streptokinase. Though less common, early recognition and prompt treatment in severe cases is crucial otherwise it will lead to morbidity of the patient[12]. The prognosis of serum sickness is quite good and used to resolve within 1-2 weeks if the offending agent is discontinued. However, repeated exposure to a causative agent have also led to renal failure and even death[5].

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Images

Table 1: Laboratory, Serological and Biochemical investigations

Figure 1: Diagnostic workup of a 36-year-old female with Serum Sickness

Declerations

1. Ethics approval and consent to participate: The Institutional Review Board of the Institute of Medicine, Nepal, does not mandate ethical approval for the writing or publication of case reports, and patient consent was obtained. Informed written consent was obtained from the patient before writing this case report.
2. Consent for publication: Informed written consent was obtained from the patient for the publication of this case report in a scientific journal.
3. Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.
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