# Enoxaparin Induced Maculopapular Rash

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## ABSTRACT

Enoxaparin is the most frequently prescribed low molecular weight heparin worldwide. It has reports of causing rare cutaneous reactions at therapeutic and toxic doses. Herein we report a case of erythematous maculopapular rashes presumed secondary to enoxaparin administration. A 65-year-old male patient diagnosed with acute coronary syndrome developed erythematous maculopapular rashes over the trunk and upper limb after receiving two doses of injection enoxaparin 40 mg. His past medical history was insignificant. The symptoms resolved two days after stopping the drug. Based on his presentation, we presume that the condition was result of enoxaparin. Causality assessment was also suggestive of a probable relationship between the patient's symptoms and use of enoxaparin.Enoxaparin can cause cutaneous adverse reactions among patients sensitive to this drug. While the pathophysiology of these cutaneous adverse drug reactions is incompletely understood, clinicians should be vigilant to allow early detection of these problems.

**Key words:** Cutaneous adverse drug reactions, Drug allergy, Enoxaparin, Geriatric, Low molecular weight heparin, Maculopapular rash.

## INTRODUCTION

Enoxaparin, the first low molecular weight heparin (LMWH) to be marketed in the United States, is derived from unfractionated heparin.[1] LMWHs are primarily used for the treatment of acute ST segment elevation myocardial infarction, deep vein thrombosis and pulmonary embolism. Adverse effects associated with enoxaparin range from nausea or vomiting to severe hemorrhages while cutaneous reactions are rare.[2] We report a case of erythematous maculopapular rash in an geriatric male patient who had no previous history of drug allergies or cutaneous reactions and was presumably caused by enoxaparin.

## ETHICAL APPROVAL

The case report below was prepared in accordance with the principles proposed in the Declaration of Helsinki. Patient was explained about the work carried out and his consent was taken on an appropriate informed consent form.

## CASE DESCRIPTION

A 65-year-old male, with a BMI of 21.3 kg/m$^2$, was admitted to a tertiary care hospital with complaints of heaviness of chest associated with sweating, blurring of vision and nausea since four hours. The patient's past medical history was suggestive of type II diabetes mellitus since three years and he was on regular treatment with tablet metformin 500 mg once daily.

On examination, his HR was 70 bpm, BP was 120/70 mmHg and RR was 16 cpm. Other systemic investigations were clinically unremarkable. Based on his complaints, a clinical diagnosis of acute coronary syndrome with type II diabetes mellitus was considered. Relevant investigations to evaluate acute coronary syndrome were advised. His fasting blood sugar, post prandial blood sugar levels and glycated hemoglobin were 195 mg/dl, 252 mg/dl and 6.9 respectively. Remaining all other laboratory parameters including the patient's troponin level, creatinine

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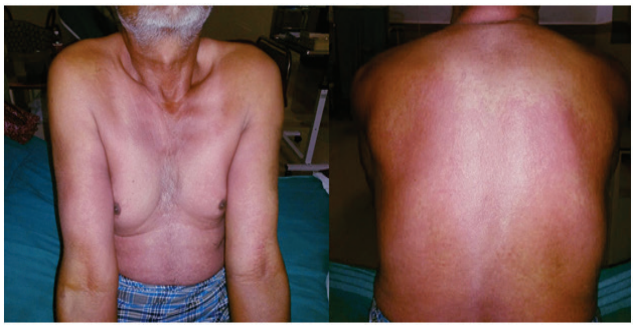

**Figure 1: Patient presenting with generalized skin rash**

kinase myocardial band and ejection fraction were unexceptional. Following admission, the patient was stabilized on injection nitroglycerin 5mcg/kg/minute stat, tablet aspirin 150 mg once daily, tablet clopidogrel 75 mg twice daily, tablet atorvastatin 40 mg once daily, injection heparin 5000 U every sixth hourly and tablet metformin 500 mg once daily. The next day injection nitroglycerin was replaced with tablet glyceryltrinitrate 2.6 mg twice daily and tablet olmesartan 40 mg once daily was also added. On the fourth day of his treatment, patient underwent coronary angiogram and his reports were suggestive of triple vessel coronary artery disease. On the seventh day, injection heparin was stopped and injection enoxaparin 40 mg twice daily was started. Based on the angiogram report, patient was subjected to angioplasty and stent implantation on the eighth day. Within hours of post angioplasty, he developed erythema and vesicles over the left forearm and erythematous tiny papules over the trunk and right upper limb (Figure 1: Patient presenting with erythematous maculopapular rash).

Dermatological opinion for the reaction was sought and the impression made as query of maculopapular rash secondary to enoxaparin. The patient was symptomatically treated with a combination of betamethasone dipropionate 0.05 % w/v and zinc sulphate 0.5% w/v lotion, tablet cetrizine 10 mg at night and injection hydrocortisone 100 mg twice daily. Following treatment, he reported a mild relief from itching but the rash was still persisting. Injection enoxaparin was then stopped on the tenth day following which the rash disappeared completely within 2 days leaving only signs of red patches which faded over the next few days. On discharge, all the remaining drugs, aspirin, clopidogrel, atorvastatin, metformin and isosorbidedinitratewere continued. Patient reported no further complaints over the one month follow-up.

The Narajo's criteria and WHO probability scale were applied to determine the causality for suspected adverse drug reaction (ADR).The causalityassessment with both scales revealed that the ADR due to enoxaparin in this case was "probable". The severity of the ADR was determined by using the Modified Hartwig and Siegel scale and was found to be moderate (level 3) reaction.

## DISCUSSION

Drug induced cutaneous ADRs, in general, are observed in approximately 1% of patients. The most frequent drug induced cutaneous reaction is a maculopapular rash.[3-4] They are characterized by raised spotted lesions which may develop within days to weeks after drug exposure, originate on the trunk and eventually spread to the limbs.[5] They may last up to two weeks after cessation of the culprit medication. The most common implicated drugs include non-steroidal anti-inflammatory drugs, anticonvulsants, allopurinol and antibiotics such as penicillins, quinolones and sulfonamides. Although they are generally not life-threatening, they can considerably reduce the quality of life of affected patients.[4]

The major adverse effects associated with LMWHs include bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase and injection site hemorrhages.[6] Although reports of rare adverse cutaneous reactions like ecchymosis, erythematous plaques and nodules have been documented, there is only one report of enoxaparin induced maculopapular rash.[1] The pathogenesis for heparin sensitivity is not completely understood, but is thought to be due to heparin acting like a hapten by binding to the dermal or the subcutaneous structural proteins and thereby triggering a delayed type 4 hypersensitivity reaction. The suspected risk factors for the development of sensitization to LMWHs are female gender, obesity, diabetes and prolonged intake of the drug.[7] In our patient, diabetes could have been one of the possible reasons for the development of rash following enoxaparin administration.

In this case, the reaction was observed after receiving two doses of enoxaparin followed by angioplasty and subsided two days after withdrawing enoxaparin. The maculopapular rash that developed over the trunk and the upper limb cannot be attributed to the iohexol dye used for the procedures, as dye used in the patient for angioplasty was used four days prior for coronary angiogram, following which there were no complaints, thus giving a safe history to it. Although other drugs like clopidogrel[8] and olmesartan[9] are also known to cause maculopapular rashes, absence of persistence of the symptoms on their continuation excludes their possible involvement. Thus in this patient, the temporal

relationship between the enoxaparin use and onset of the maculopapular rash and its resolution when the drug was stopped, strongly implicate enoxaparin as the sole responsible agent for the suspected reaction.

## CONCLUSION

Although cutaneous reactions are known to occur with enoxaparin, reports of maculopapular rashes are rare. Thus, this case report of enoxaparin induced maculopapular rash adds more value to the existing data. It also helps to create awareness about the various risk factors associated with the development of rashes. Clinicians should be more vigilant for any signs of adverse effects with enoxaparin, so that a safer alternative can be started. They should also educate the patients to identify and promptly report any adverse drug reactions.

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## CONFLICT OF INTEREST

The authors report no conflict of interest that is directly relevant to the content of the case report.

## ABBREVIATION USED

| | |
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| ADR: | Adverse Drug Reaction |
| BMI: | Body Mass Index |
| BP: | Blood Pressure |
| HR: | Heart Rate |
| LMWH: | Low Molecular Weight Heparin |
| RR: | Respiratory Rate |
| WHO: | World Health Organization |

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