

Clinical quiz: an old lady with oedema of all four limbs

臨床猜謎：一名四肢水腫的老婦

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Case

A 68-year-old lady attended the clinic early this year for bilateral upper and lower limb oedema for about two weeks.

Apart from hypercholesterolemia, she otherwise had enjoyed good past health. Recently she was disturbed by swelling in all four limbs in the past two weeks. The swelling was mainly located in the hands, fingers and ankles which was affecting her movement. The symptom was associated with general malaise, weakness and mild breathlessness on exertion. She felt that she was "heavier" than before, despite there being no objective weight gain. There was no orthopnoea or paroxysmal nocturnal dyspnoea. Neither nocturia nor frothy urine was found. No systemic upset was noted and her appetite was good.

The general examination revealed that the oedema was located as mentioned. Systemic examinations did not show any particular alarming feature. Cardiovascular, thyroid status, respiratory, abdominal and neurological examinations were all unremarkable. Her blood

pressure and pulse rate were 130/70 mmHg and 80 beats per minute respectively. In the light of her clinical condition, she was admitted to a private hospital for investigation.

Complete blood picture, renal function test, liver function test, creatine kinase-MB, troponin I, B-type natriuretic peptide and thyroid function profile were all normal. Urine for microscopy was clear and no haematuria or proteinuria was noted. Chest radiography, resting electrocardiography, echocardiogram, Holter monitoring and ultrasound of both kidneys were unremarkable. Computed tomography of the abdomen and pelvis did not reveal any malignancy or space-occupying lesion.

Questions

1. Name one clinical history of the patient that should be elicited.
2. What is your presumptive diagnosis?
3. Which blood test you would like to perform to confirm your diagnosis?

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Answers

1. Drug history: she is taking Crestor (rosuvastatin) 10 mg daily for hypercholesterolemia
2. Presumptive diagnosis: statin-induced peripheral oedema and myopathy.
3. Blood test: serum myoglobin. The serum myoglobin was 128.1 ng/ml (reference range: 0-61 ng/ml)

The patient suffered from statin-induced peripheral oedema, myopathy and hypermyoglobinemia. The statin was discontinued immediately when hypermyoglobinemia was noted. The swelling and muscle weakness resolved after the cessation. The serum myoglobin repeated one week later was normal. She was then able to walk upstairs without difficulty.

Discussion

Statin was first invented by a Japanese scientist Akira Endo who found that the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase was inhibited by a fungal metabolite.¹ Statins, one of the best-selling medications worldwide, is classified into three generations. The first generation includes lovastatin, pravastatin and fluvastatin. The second generation includes simvastatin and atorvastatin. Rosuvastatin belongs to the third generation.

Encompassing a blend of unique chemical structures, rosuvastatin is one of the most potent statins. First, it has a fluorinated phenyl group and a polar methane sulphonamide group. This chemical structure offers strong and multiple antagonistic effects on HMG-CoA. In addition, the binding strength between rosuvastatin and HMG-CoA is enhanced due to the presence of short hydrogen bond length after binding. The hydrophilic nature offers the final advantage by reducing unnecessary metabolic drug interaction.

The incidence of myopathy and peripheral oedema in the Rosuvastatin Clinical Study Program was reported to be less than 1%. The reported adverse events occurred usually in patients taking 40 mg to 80 mg of rosuvastatin. The higher the dose, the greater the risk of adverse events. However, myopathy and

hypermyoglobinemia had been reported in patients using 10 mg only.² The mechanism for myopathy comes about because statins decrease the beta-oxidation, glutamate-driven state 3 respiration and respiratory control ratios in skeletal muscle mitochondrial functions. Rosuvastatin is considered to be much less toxic than the other statins as it impacts less on the mitochondria.³

The diagnostic criteria of myopathy is theoretically defined as referring to any muscular discomfort associated with more than 3-10 times increase in creatine kinase level.^{1,4} Nevertheless, in actual clinical situations, the most common side effect of statins remains myalgia without change in creatine kinase level.⁵

Precipitating factors for statin-induced adverse events include old age, impaired renal function, alcoholism, hypothyroidism, concomitant infections and drug interactions, such as fibrates, warfarin, digoxin, macrolide antibiotics, niacin, antifungals, and cyclosporine.⁶

Other infrequent adverse events include:

- Musculo-skeletal: abdominal pain, chest pain, muscle pain.
- Cardiovascular: hypertension.
- Gastrointestinal: diarrhoea or constipation.
- Metabolic: peripheral oedema.
- Peripheral nervous system: dizziness, insomnia, depression, numbness.
- Respiratory system: bronchitis, persistent flu syndrome, shortness of breath, exertional dyspnoea.

Statins are very commonly prescribed medications throughout the world. Peripheral oedema is not necessarily an internal organ problem, but one due to the effects of drugs. In this case, drug history was of paramount importance and the clinical diagnosis was made firstly, by the integration of her clinical picture with hypermyoglobinemia and secondly, by the elimination of other differentials. The high index of suspicion of this condition should be raised especially when elderly patients present with vague and non-specific symptoms. If unrecognised in its early

manifestations, prolonged statin usage could induce fatal rhabdomyolysis.⁶

References

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