**Rhabdomyolysis triggered by azithromycin**

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**Abstract**

A 17-year-old male with uneventful previous history developed generalized myalgias, exercise intolerance, and general fatigue after two dosages of azithromycin (500 mg/d) during 3 d for febrile infection. Neurologic exam revealed generally reduced tendon reflexes. Serum creatine kinase (CK) was elevated to 25000 U/L. Needle-EMG showed short and small, polyphasic motor-units and abnormal spontaneous activity, being interpreted as myositis. Azithromycin was discontinued and he was advised to avoid the fitness studio and to drink plenty of liquids. Myalgias disappeared within two days and CK continuously declined. Azithromycin may trigger rhabdomyolysis in the context of exercise and infection. Azithromycin may be myotoxic and should be prescribed with caution in exercising and infected patients.

**Keywords:** Adverse reaction, creatine kinase, macrolid antibiotics, myopathy, rhabdomyolysis

**Introduction**

Rhabdomyolysis results from a wide variety of conditions such as trauma, exercise, infection, myopathy, or drugs.¹ In pediatric patients, the most frequent causes are infection, exercise, and primary myopathies.¹,² Rhabdomyolysis in a pediatric patient triggered by exercise, infection, and the macrolid azithromycin without any co-medication has not been reported. The reported subject gave written informed consent and patient anonymity was preserved.

**Case Report**

The patient is a 17-year-old Iranian male with an uneventful previous history. Until 7 days prior to admission, he was regularly doing sports (volleyball, football) and visited a fitness studio 4 times a week since 1.5 years without complications so far and without taking hormones or dietary supplements. He had attended the office of his GP because of abdominal pain, nausea, emesis, and fever (38.5°C) 9 days prior to admission. The GP prescribed azithromycin 500 mg/d for 3 days. Blood tests one day later revealed elevated transaminases (GOT: 396 U/L, GPT: 555 U/L), which is why he was referred to the hospital. After having taken 2 dosages of azithromycin (7 days and 6 days prior to admission), the patient attended the hospital's emergency ward because of generalized myalgias. CK was markedly elevated [Table 1]. Azithromycin was discontinued and he received fluid intravenously and was asked to drink much and to stop sports. Two days later abdominal pain, nausea, vomiting, and myalgias had disappeared and CK values showed a tendency to decline [Table 1]. Another two days later he was still symptom-free and CK had further declined [Table 1]. One day before admission he had developed generalized fatigue, tiredness and dyspnea. CK showed a tendency to increase again. Since CK further increased on the next day, including the CK-MB fraction, he was admitted to the cardiology department, where myocardial infarction was excluded.

The family history was positive for consanguninity of the parents, which were first degree cousins and for polymyositis in...
Among infections, particularly viral infections may trigger rhabdomyolysis. Viruses known to trigger rhabdomyolysis include Adeno, Influenza-A, Influenza-B, Cytomegaly, Epstein-Barr, Coxsackie-B, Parvo, Noro, HIV, Dengue, Chikungunya, Ebola, and Zika virus. Bacteria or protozoa causing rhabdomyolysis include *Staphylococcus, streptococcus, Klebsiella, Listeria, Salmonella, mycoplasma pneumonia, Treponema pallidum, Morganella morgani, Brucella, or Leptospira*. In the presented patient, fever was most likely due to a viral infection, although virological investigations were carried out. Exercise triggering rhabdomyolysis may be strenuous, moderate, or mild. If there is an underlying myopathy, even mild exercise may trigger severe rhabdomyolysis. Most frequently, however, exercise-induced rhabdomyolysis occurs after high intensity workout programs.

Since statins are known to cause mitochondrial myopathy in about 1% of those taking statins,[9] it can be speculated that azithromycin triggers rhabdomyolysis only in patients with subclinical or mildly manifesting myopathy. Since the presented patient was not taking any medication known to cause myopathy, it can be speculated that he was suffering from subclinical primary myopathy. Arguments for subclinical myopathy in the presented patient are that needle-EMG was myogenic, that tendon reflexes were reduced, and that the family history was positive for polymyositis. Assuming that polymyositis in his uncle was in fact a misdiagnosed primary myopathy, it is quite likely that infection plus exercise and azithromycin triggered rhabdomyolysis in the presented case. Work-up for subclinical myopathy, particularly metabolic myopathy, was indicated not only because of rhabdomyolysis and the family history but also because of the generally reduced tendon reflexes and the myogenic EMG, which were not explained by rhabdomyolysis. Primary myopathies, which may be complicated by rhabdomyolysis, include glycogen storage diseases, lipid storage diseases, beta-oxidation defects, respiratory chain disorders, and congenital muscular dystrophies.[9]

This case shows that azithromycin may trigger rhabdomyolysis in the context of exercise and infection, that subclinical myopathy may favor the rhabdomyogenic effect of triggering compounds, and that azithromycin should be prescribed with caution in exercising and infected patients if the family history is positive for neuromuscular disorder.

### Discussion

The presented patient is interesting for rhabdomyolysis triggered by exercise, infection, or azithromycin. Which of these conditions or which combination had the strongest triggering effect remains speculative. Drugs prone to trigger rhabdomyolysis are macrolide antibiotics.[8] Supposing that rhabdomyolysis was triggered by azithromycin alone, this has not been reported before and represents a new finding. Though rhabdomyolysis after azithromycin has been repeatedly reported, all these patients were contrary to the index case under another medication in addition to azithromycin, particularly statins or cyclosporine.[4,8] Azithromycin in general exerts its action by blocking the protein synthesis of various bacteria. Additionally, azithromycin is known to inhibit P-glycoprotein with the consequence of reducing hepatic and urine excretion.[5] Macrolids also inhibit the CYP metabolism. Patients taking statins not metabolized by CYP3A4 and a macrolid have an increased risk of hospital admission for acute kidney failure and rhabdomyolysis.[4] The paper is relevant for primary care physicians as they are frequently confronted with rhabdomyolysis and its management. Primary care physicians are forced to identify the trigger of rhabdomyolysis and to manage these patients. This case shows that azithromycin is a potential trigger of rhabdomyolysis and that discontinuation of this trigger can be beneficial.

### Table 1: Results of blood tests during hospitalisation

| Hd   | RL   | -7  | -6  | -5  | -3  | -1  | 1   | 2   | 3   | 4   | 5   |
|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| CK   | <190 U/L | 25122 | 24303 | 20882 | 19429 | 20509 | 24588 | 18545 | 17862 | 16786 | 15917 |
| GOT  | 10.50 U/L | 448 | 435 | 404 | nd | 454 | nd | 354 | 347 | 319 |
| GPT  | 10.50 U/L | 542 | nd | 536 | 484 | 506 | 505 | 425 | 424 | 440 | 442 |
| Creatinine | 0.7-1.2 mg/dl | 0.7 | nd | 0.61 | nd | 0.67 | 0.7 | 0.66 | 0.68 | 0.72 | 0.56 |
| GFR | >90 mL/min/1.7 m² | 147 | nd | 172 | nd | 153 | 147 | 157 | 152 | 142 | 190 |
| Troponin-T | <14 ng/L | nd | nd | nd | 149 | 136 | 198 | 129 | 142 | nd | 130 |
| Sodium | 136-145 mmol/l | 141 | nd | nd | nd | nd | nd | 140 | 135 | 140 | 139 | 142 |
| Potassium | 3.4-4.5 mmol/l | 4.3 | nd | nd | nd | nd | nd | 4.3 | 4.4 | 4.5 | 4.4 |
| CRP | <5.0 mg and L | 8.2 | nd | 2.7 | nd | nd | nd | 0.4 | 0.4 | 0.8 | nd |
| Aldolase | 0-7.6 U/L | nd | nd | nd | nd | nd | nd | nd | nd | nd | 160 |

Hd: Hospital day; RL: Reference limit, CK: Creatine kinase, GOT: Glutamate-oxalate transaminase, GPT: Glutamate-pyruvate transaminase, GFR: Glomerular filtration rate, nd: Not done
Ethical approval
The study was approved by the institutional review board.

Declaration of patient consent
The reported subject gave written informed consent and patient anonymity was preserved.

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Conflicts of interest
There are no conflicts of interest.

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