Statins and ribociclib interaction induced necrotising myopathy: a case report and literature review

Dear Sir,

We present the case of a 74-year-old female that was referred to the Emergency Department of our hospital for dyspnoea and tachycardia. She reported significant limitations in physical activity and progressive weakness in her lower limbs over the past two months. Her medical history included atrial fibrillation in treatment with edoxaban, osteoporosis, and hypercholesterolemia treated with Simvastatin 20 mg daily. Of note, two months earlier she had been diagnosed with breast cancer with pleuro-pulmonary metastases, complicated by massive left pleural effusion. A breast tissue biopsy showed a G2-graded, HER2+ and ER+ invasive carcinoma, for which she was prescribed ribociclib (a CDK4/6 inhibitor) (1) 600 mg/die and Letrozole 2,5 mg/die one month prior. At admission, she presented with tachyarrhythmia, while no significant muscular weakness was detected. However, after four days, her clinical condition worsened, with the development of widespread oedema, especially in the limbs, dysphagia for solids, and a marked elevation of muscular enzymes with creatine kinase (CK) up to 15900 U/L. Antineoplastic therapy and statins were promptly discontinued. A neurologic evaluation showed severe proximal weakness, especially in the lower limbs. Electromyography (EMG) showed a neurogenic pattern in gastrocnemius muscle, without signs of acute denervation. In accordance with immunologists, high-dose steroid therapy (prednisone 100 mg/die) was initiated, and a muscle biopsy was performed, revealing diffuse fibres necrosis (Fig. 1). Muscle MRI was consistent with myositis, showing significant oedema in all muscles, perifascial fluid effusion, and subcutaneous oedema (Fig. 2). The patient was also found to have a hypotonic upper oesophageal sphincter and oesophageal hypokinesia on upper gastrointestinal study. Echocardiogram revealed systolic heart failure and diffused left ventricular hypokinesis. Unfortunately, despite the normalisation of CK levels, her clinical conditions continued to deteriorate, with progressive worsening of weakness, dysphagia, and oedema, ultimately leading to her death.

Ribociclib is an oral selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor used in the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer (2). In association with an aromatase inhibitor (AI), it was approved for patients with advanced or metastatic cancer (3). In September 2024, the U.S. Food and Drug Administration (FDA) expanded the indication for ribociclib to include adjuvant treatment for adults with HR+, HER2- early breast cancer at high risk of recurrence, in combination with an aromatase inhibitor,

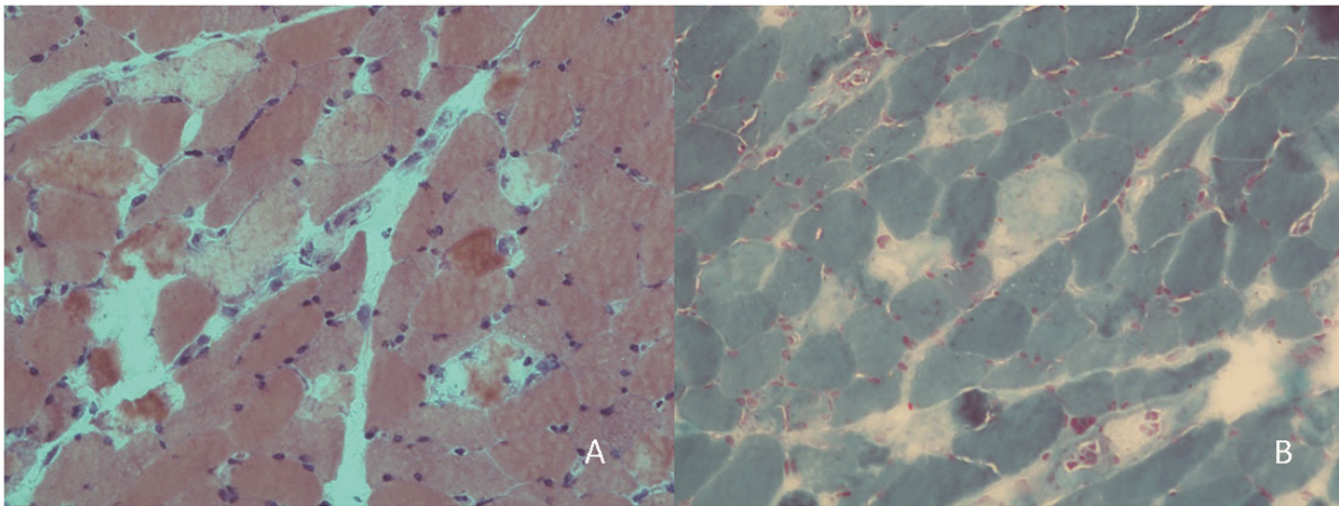

Fig. 1. Muscle biopsy: (**A**) Ematoxilin-Eosin staining, 20X; (**B**) Gomori Trichrome staining, 20X.

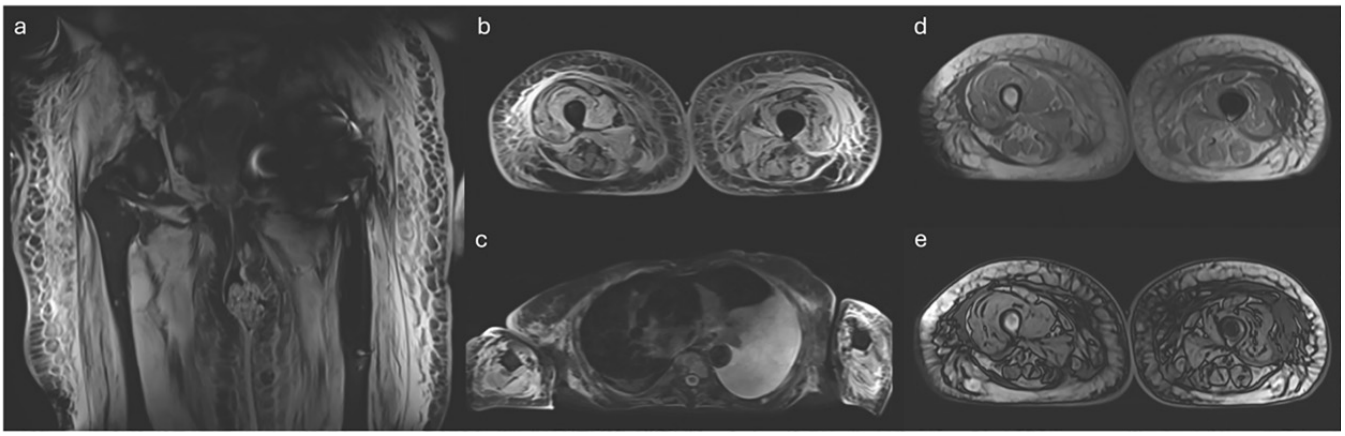

Fig. 2. Muscular MRI showing diffuse muscular oedema of thighs and arms, in particular diffuse muscular bellies hyperintensity is depicted on coronal (**A**) and axial (**B**) STIR at the level of the thighs and on axial STIR (**C**) at the level of the arms. On these images, also fluid epimysial collection and diffuse subcutaneous fat oedema are displayed, especially at thighs' level. On the right, axial dual-echo images at the level of the thighs show minimal intramuscular signal drop from in-phase (**D**) to out-of-phase (**E**) images representing minimal fat infiltration in all thighs' muscles.

Table I. Summary of reported cases of rhabdomyolysis associated with concomitant use of statins and ribociclib.

Reference	Patient characteristics	Outcome
Teo *et al*., 2023 (6)	Woman in her sixth decade of life with HR+/HER2- breast cancer, spinal metastasis, stage 3A chronic kidney disease, and a history of stroke. On ribociclib (200 mg, 3 weeks on/1 week off for 4 years), anastrozole, and rosuvastatin (10 mg daily).	Developed rhabdomyolysis with CK 3608 μg/L, AKI (eGFR decline from 45 to 8 mL/min), myoglobinuria, confusion, fever, and myoclonic twitching. Myositis blot and HMG-CoA reductase antibodies were negative. Managed with supportive care. Statin therapy was discontinued, leading to normalisation of CK levels and restoration of eGFR to baseline.
Streicher *et al*., 2021 (7)	68-year-old woman with HR+/HER2- metastatic breast cancer on prior Simvastatin therapy with a history of hypercholesterolemia and hypertension. On therapy with ribociclib 600 mg daily (3 weeks on/1 week of) and letrozole for 3 weeks.	Developed severe rhabdomyolysis presenting with progressive weakness, myalgia and confusion. Ribociclib and Simvastatin were discontinued, and the patient received intensive intravenous hydration. Mobility recovered after two weeks.
Badran *et al*., 2023 (8)	73-year-old woman with HR+/HER2- breast cancer, hypertension, atrial fibrillation, hyperlipidaemia and diabetes. On therapy with Simvastatin 40 mg for several years prior, she had been taking ribociclib (600 mg/day) for recurrent breast cancer with bone metastases for one year and a half.	Developed rhabdomyolysis with acute kidney injury. Ribociclib and simvastatin were discontinued, IV fluids administered. Renal function improved, ribociclib reintroduced at 200 mg/day, simvastatin permanently discontinued.

Search strategy used to retrieve references from Pubmed: ribociclib AND statins AND rhabdomyolysis.

thus increasing the number of patients that could undergo such treatment (4). Side effects of ribociclib include neutropenia, fatigue, nausea, diarrhoea, and elevated liver enzymes. Notably, in the most recent report on the drug's safety profile, only "blood creatine" increased values, dyspnoea and fatigue are reported as possible muscular involvement signs, without a specific warning for it (5). Three more cases of severe rhabdomyolisis in patients undergoing concomitant treatment with statins and ribociclib have been described and are summarized in Table I (6-8). Ribociclib is a CYP3A4 inhibitor, thus possibly interacting with other drugs which are metabolised via CYP3A4 (9), as simvastatin, whose circulating levels may thus be increased (10). Rhabdomyolisis is a well-known and potentially severe side effect of statins (11) and the concomitant use of ribociclib may lead to an accumulation of statins and to a dangerous enhancement of their side effects. Given the high prevalence of breast cancer patients receiving CDK4/6 inhibitors and the widespread use of statins, we believe that these cases should prompt a thorough data collection about baseline characteristics of patients to identify potential risk factors, as well as a systematic evaluation of clinical outcomes. Additionally, careful consideration should be given to switching from statins to alternative lipid-lowering drugs, which are nowadays available, when clinically appropriate.

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