

# A rare adverse effect while treating lung adenocarcinoma

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#### Key Words:

- Lung adenocarcinoma
- Rhabdomyolysis
- Bevacizumab

**ABSTRACT.** Rhabdomyolysis is a syndrome resulting from acute skeletal muscle necrosis, with subsequent massive release of muscle cell components into the circulation. Although the pathophysiology as well as the clinical aspects of rhabdomyolysis have been quite well investigated, the physician should be alert in case a patient presents with the syndrome, as it may be complicated with acute kidney injury which increases mortality. In addition, the causes of rhabdomyolysis are multiple, with drugs being responsible most of the times. In the field of oncology, the complexity of patients' symptoms and the continuous introduction of new medicines make the diagnosis of any clinical entity challenging. The oncologist should always include rhabdomyolysis in the differential diagnosis of related symptoms (the classic triad of myalgias, muscle weakness and urine hyperpigmentation). Early treatment decreases the duration of rhabdomyolysis and may prevent acute kidney injury. Bevacizumab is an anti-VEGF agent indicated in the treatment of numerous neoplastic diseases. Rhabdomyolysis is not usual after chemotherapy or monoclonal antibody administration. We observed and here present a case of rhabdomyolysis after bevacizumab therapy in a patient with non-small cell lung cancer and we subsequently review the aspects of rhabdomyolysis. Our aim is to alert physicians treating oncology patients in rhabdomyolysis, as a rare adverse effect of anticancer drugs. *Pneumon 2015, 28(3):262-265.*

## CASE REPORT

A male patient, aged 82, presented with muscle pain and intense weakness of the lower extremities, one day after taking bevacizumab as maintenance therapy for pulmonary adenocarcinoma. The patient did not report intense muscular activity before the incidence or taking any other drug except for bevacizumab. The physical examination did not reveal any evidence of trauma. Muscle strength of the lower extremities was measured 2/5 bilaterally, while no sensory or tendon reflex disorders were observed.

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Motor activity and strength of the upper extremities were normal. Vital signs were normal as well.

The urgent brain and cervical spinal cord CT scan were negative for metastasis or acute vascular incident. The ECG and the triplex of lower extremities presented no evidence of acute cardiovascular incident. From the laboratory tests an increase of the creatine phosphokinase (CPK) up to 3953 U/l and incipient renal failure (urea 95 mg/dl, creatinine 1.83 mg/dl, uric acid 13.6 mg/dl) were noted. The urine stick was positive (+++) for red blood cells and the colour of urine was brown. Our patient was diagnosed with rhabdomyolysis. The immediate measures included bladder catheter placement, hydration with 3 liters of Natural Saline 0.9% per 24 hours and allopurinol 300 mg daily. Five days after diagnosis: creatinine 1.1 mg/dl, urea 44 mg/dl and CPK 149 U/l. A few days later the patient was dismissed.

## DISCUSSION

### Etiology and pathophysiology

Rhabdomyolysis is a syndrome resulting from acute skeletal muscle necrosis. The pathophysiology of rhabdomyolysis starts with muscle cell membrane rupture and/or reduced energy production. Both situations lead to increase of the intracellular ionized calcium, resulting to muscle cell damage.<sup>2</sup> The final result is the release of intracellular components into the circulation: enzymes (CPK, lactate dehydrogenase, aspartic transaminase, aldolase), proteins (myoglobin), purin products (uric acid) and electrolytes (potassium, calcium, phosphorus). The skeletal muscles of the extremities are more sensitive to injury and hypoxia due to their peripheral position. The causes of rhabdomyolysis are shown in the Table. Today, most cases of rhabdomyolysis are a result of drugs intake.<sup>1</sup>

The most important complication of rhabdomyolysis is the Acute Kidney Injury (AKI). The mechanisms contributing to AKI development are: a) the sedimentation of myoglobin in the renal tubules, b) the constriction of the renal arteries due to extracellular volume reduction and c) the production of free oxygen radicals. Myoglobin precipitates at high concentrations, especially when hypovolemia also exists. At pH <5.6 myoglobin decays giving hemosiderin, which results to free radicals production and oxidative damages to the renal parenchyma. The kidney damage may deteriorate due to uric acid crystals sedimentation and co-existing electrolyte disorders.

### Clinical presentation, diagnosis and treatment

Clinically, the classic triad of rhabdomyolysis consists of myalgias, muscle weakness and urine hyperpigmentation, although all symptoms may not be always present. Muscles usually participating are these of the lower extremities and the lumbus. The patient may refer weakness, pain, a sense of heaviness or tension, especially in the lower extremities; however, these symptoms are not specific. The clinical presentation is completed by the symptoms and signs of the underlying cause. Dehydration, electrolyte disorders and renal insufficiency may cause nausea, vomiting, cardiac arrhythmias and consciousness disorders.

The CPK rates may be elevated by 5 or more times from normal. Serum CPK increases during the first 12 hours, reaches the peak values at 24-72 hours and subsequently decreases with a rate of 30-40% daily (provided that muscle necrosis has stopped). Higher levels of CPK associate with a higher degree of or prolonged muscle necrosis and seem to relate to the risk of AKI development and mortality. Myoglobin is excreted in the urine and in concentrations higher than 100 mg/dl it colours the urine brown. It causes a positive reaction at the urine stick because it contains the heme ring. In case the urine stick is positive for blood, whereas there are no erythrocytes in the urinalysis, then myoglobinuria is suspected. However, a negative result does not exclude the diagnosis of rhabdomyolysis as myoglobin is eliminated by the plasma within 1-6 hours from muscle damage.

The risk of AKI after rhabdomyolysis is higher when the CPK levels are higher than 5000 IU/l and creatinine more than 1.5 mg/dl. The mortality rates are generally higher in patients with rhabdomyolysis which is complicated with renal insufficiency. The immediate hydration with at least 3 liters of fluids per 24 hours may be sufficient for preventing the AKI. The addition of bicarbonates in the administered fluids may ameliorate the acidosis, as well as contribute to the alkalization of the urine, resulting in the limitation of myoglobin and uric acid sedimentation in the renal tubules. The administration of mannitol and loop diuretics may be helpful to some patients, but it is not recommended at the initial management of rhabdomyolysis.<sup>1</sup>

### Causes of rhabdomyolysis

#### *Rhabdomyolysis and bevacizumab*

After excluding the most possible causes of rhabdomyolysis in our patient, we considered the possibility of

<b>Physical</b>	<b>Chemical</b>	<b>Biological</b>
Hypoxia	Drugs	<b>Organic toxins</b>
CO or cyanides poisoning	Statins & fibrates	Infections
Compartment syndrome	Antipsychotics	Bacteria
Prolonged immobilization	SSRIs	Gram +
Thrombosis/Embolism	Antibiotics	Legionella
Diffuse microcirculation obstruction	Amphotericin B	Salmonella
Vasculitis	Antimalarials	Viruses
Sickle cell trait	Daptomycin	Influenza A/B
Septic shock	Quinolones	Enteroviruses
	Macrolides	HIV
<b>Traumatic</b>	SMX/TMP	Herpes virus
Muscle crushing:	Antiretrovirals	Coxsackie virus
Natural disasters	Protease inhibitors	Parasites
Car/working accidents	Anesthetics	Plasmodium species causing malaria
Abuse	Propofol continuous infusion	Spider/snake poisons
Intense muscle exercise	Antiemetics	Insect bite
Electric shock	Metoclopramide	
Seizures	Antihistamines	<b>Diseases</b>
Delirium tremens	Colchicine	Endocrinopathies
Status asthmaticus	Abiraterone	Adrenal insufficiency
Hyperthermia	Adalimumab	Hypothyroidism
Heat stroke	Alcohol	Hyperaldosteronism
Neuroleptic malignant syndrome	Narcotics	Polymyositis/ Dermatomyositis
Malignant hyperthermia	Heroin	Hereditary metabolic myopathies
	Cocaine	McArdle disease
	Amphetamines	Deficiency of the mitochondrial respiratory chain enzymes
	Illusive drugs	Carnitine palmityl transferase deficiency
		Phosphofructokinase deficiency
	<b>Electrolytes</b>	AMP aminase deficiency
	Hypopotassemia	
	Hypophosphatemia	
	Hypocalcemia	
	Hyponatremia	
	Hypernatremia	
	Hyperosmotic state	
	Diabetic ketoacidosis	

bevacizumab being responsible. Bevacizumab is a recombinant humanized monoclonal antibody that produces angiogenesis inhibition by binding to and blocking the vascular endothelial growth factor (VEGF). Bevacizumab

is used in the treatment of numerous neoplastic diseases, including the locally advanced or metastatic non-small cell lung cancer.

Rhabdomyolysis is not usual after chemotherapy and

it is rare after monoclonal antibody administration. The chemotherapeutic agents that have been associated with rhabdomyolysis cases are cytarabine, paclitaxel, gemcitabine, trabectedin and pemetrexed.<sup>3-6</sup> Rhabdomyolysis has been referred after treatment with the monoclonal antibodies rituximab and adalimumab.<sup>8</sup> Concerning anti-angiogenic agents, there has been a small number of rhabdomyolysis cases in patients receiving sunitinib or erlotinib (tyrosine kinase inhibitors).<sup>9</sup> Among the adverse events of bevacizumab there is muscle weakness, but there is no reference to CPK increase or rhabdomyolysis.<sup>10</sup>

## CONCLUSION

Rhabdomyolysis is not usual after chemotherapy or monoclonal antibody administration. When treating oncology patients, the complexity of their symptoms and the continuous introduction of new medicines make the diagnosis of any clinical entity challenging. These patients may present with various musculoskeletal symptoms, either due to the disease itself, or due to adverse reactions caused by the administered drugs. Physicians should always include rhabdomyolysis in the differential diagnosis of related symptoms. Early treatment decreases the duration of rhabdomyolysis and may prevent acute kidney injury.

## REFERENCES

1. Zimmerman JL, Shen MC. Rhabdomyolysis. *Chest* 2013; 144:1058-65.
2. Vanholder R, et al. Rhabdomyolysis. *J Am Soc Nephrol* 2000; 11:1553-61.
3. Huang MS, Tsai JR, Shen MC, Chou SH, Yang CJ. Pemetrexed as a possible cause of severe rhabdomyolysis in the treatment of lung cancer. *Lung Cancer* 2012;76:491-2.
4. Truica CI, Frankel SR. Acute rhabdomyolysis as a complication of cytarabine chemotherapy for acute myeloid leukemia: case report and review of literature. *Am J Hematol* 2002;70:320-3.
5. Vicente E, et al. Acute rhabdomyolysis as a complication of paclitaxel-gemcitabine chemotherapy for ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 2009;145:226.
6. Stoyianni A, et al. Trabectedin-related rhabdomyolysis: an uncommon but fatal toxicity. *Tumori* 2011;97:252-5.
7. Valiyil R, Christopher-Stine L. Drug-related Myopathies of Which the Clinician Should Be Aware. *Curr Rheumatol Rep* 2010;12:213-20.
8. Ramamoorthy SK. Unusual reaction to Rituximab with intravascular hemolysis, rhabdomyolysis, renal failure and bone marrow necrosis. *Leuk Lymphoma* 2006;47:747-50.
9. Ruggeri EM et al. Severe rhabdomyolysis during sunitinib treatment of metastatic renal cell carcinoma. A report of two cases. *Annals of Oncol* 2010;21:1926-7.
10. Hurwitz HI et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: Pooled analysis from seven randomized controlled trials. *Oncologist* 2013;18:1004-12.