Radiologic Findings in Gabapentin-Induced Myositis

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ABSTRACT

Throughout recent years, Gabapentin has become increasingly used for the treatment of neuropathic pain. We report on a case of a 31 year old female who presented to the emergency department with unilateral leg pain, weakness, and swelling after increasingly titrating her Gabapentin dosage over three weeks. Magnetic resonance imaging confirmed the presence of myositis confined to the left thigh and the patient's symptoms and laboratory abnormalities resolved following Gabapentin cessation. While Gabapentin-induced myositis and rhabdomyolysis is a rare entity, it should be a diagnostic consideration for radiologists, particularly in the absence of infection or trauma.

CASE REPORT

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A 31 year old female presented to the emergency department (ED) with left thigh pain and increasing leg circumference, which began one day prior to presentation. She had woken up with generalized stiffness and with both legs and arms in flexion requiring assistance for full extension. The patient also reported left leg weakness, pain and loss of sensation. There was no history of prolonged lower extremity immobilization prior to admission, nor was there a history of trauma or injury otherwise to the left leg. No clinical evidence was present to suggest underlying infection or cellulitis. The patient denied any fever, diaphoresis, nausea, vomiting, memory loss, or drug intoxication. Her past medical history included bipolar disorder, prior substance abuse, remote trauma (motor vehicle accident), and sciatica secondary to nerve impingement. There was no history of diabetes or renal impairment. Her medications on admission were: Hydromorphone, Naproxen, Gabapentin, Trazodone, Paroxetine, and Bupropion. She had been compliant with her medications with no alterations in dosages, except for her Gabapentin, which had been titrated from 1200 mg to 3000 mg once daily over the 3 weeks preceding her presentation. No allergies or history of an adverse drug reaction were reported.

Upon admission to the ED, the patient's Gabapentin was discontinued and her Hydromorphone and Naproxen were continued for pain control along with all psychotropic medications (Trazadone, Paroxetine, Bupropion). After initial assessment in the ED, multiple clinical services were consulted.

On examination by the Neurology service, there was found to be diffuse pain from the left buttock to the left knee along with mild associated muscle weakness (4/5) on knee flexion. The patient also experienced pain with internal and external rotation of the left hip. Tone and muscle bulk were normal bilaterally and peripheral pulses were present and unremarkable. The patient exhibited impaired sensation to touch on the lateral aspect of the left leg.

Orthopedic and Vascular Surgery consultations reported full range of motion, supple muscles in the left buttock, thigh and calf with no evidence of vascular compromise. The decision to not obtain compartmental pressures was made given that the clinical findings were not in keeping with a diagnosis of compartment syndrome.

The patient's bloodwork showed an elevated creatine kinase of 44360 U/L (reference range: 38-176 U/L). Her renal function tests were normal and urine toxicology immunoassay was negative. The patient's white cell count was 3.4 x109 (reference range: 4.0-11x109), hemoglobin 138 g/L (reference range: 120-155 g/L), platelets 126x109 (reference range: 150-400x109), and her electrolyte panel was within normal limits. CRP was elevated at 8 mg/L (reference range: <3.1 mg/L) as was her lactate dehydrogenase at 1172 U/L (reference range: 90-240 U/L).

Given the unilateral nature of this presentation, the initial diagnostic imaging test ordered was an ultrasound of the left lower extremity. Doppler ultrasound demonstrated normal laminar flow through the venous and arterial structures with diffuse areas of hypoechogenicity in the subcutaneous tissues of the left medial thigh, compatible with edema (Fig. 1). With a negative Doppler ultrasound, the next diagnostic imaging test ordered was a CT angiogram (CTA). There was no evidence of vascular compromise or nerve compression on CTA, however, a hypoattenuating lesion was seen in the adductor compartment of the left medial thigh (Fig. 2).

MRI with administration of intravenous contrast using 7 cc of Gadovist (Gadobutrol) was subsequently performed for further characterization. Profound subcutaneous and muscular edema was noted throughout the left thigh on T2 fat suppressed (FS) inversion recovery images (Fig. 3 and Fig. 4). The patient's legs measured 22.9 cm and 17.4 cm on the left and right, respectively (Fig. 3). The increased T2 signal involved the adductor magnus, tensor fascia lata, vastus lateralis, gluteus medius, and gluteus maximus and was felt to be most compatible with inflammatory changes (Fig. 3, Fig. 4). Moreover, there was tracking of this fluid along the muscle compartments, which was best demonstrated on axial images (Fig. 5). On post-contrast T1 FS sequences, heterogeneous enhancement was seen involving the gluteus maximus, adductor magnus, tensor fascia lata, and gracilis muscle (Fig. 6 and Fig. 7).

This patient was closely observed by the medical team and received aggressive IV fluid resuscitation. After cessation of Gabapentin and IV hydration, the patient's creatine kinase levels dropped to 4000 U/L (reference range: 38-176 U/L) within 24 hours. The patient was discharged with a recommendation for Gabapentin to be avoided in the future. Short-term clinical follow up and outpatient laboratory studies showed a normal creatine kinase level and symptom resolution.

DISCUSSION

Etiology & Demographics:

Drugs that are well known to cause rhabdomyolysis include: Atorvastatin, Simvastatin, Interferon alpha-2b, antimicrotubule chemotherapy agents (ie: Gemcitabine), protease inhibitors (ie: Saquinavir), and mitochondrial toxins [1-5]. The three primary mechanisms in which rhabdomyolysis induction occurs are: impaired autophagy, metabolic impairment, or medication induced autoimmune reactions [2].

Gabapentin is a second generation antiepileptic drug that been increasingly used for the treatment of neuropathic pain. In fact, it has become a first line treatment for neuropathic pain as per many societal guidelines, including the Canadian Pain Society [6]. In the setting of neuropathic pain, Gabapentin dampens neuronal excitability via calcium channel modulation to provide pain relief [7]. Common side effects of Gabapentin include ataxia, drowsiness, fatigue, and dizziness [7,8]. Myositis and rhabdomyolysis, however, are a very rare side effect of Gabapentin use, and to our knowledge, there have been only six reported cases in the current literature [9-13]. Given that Gabapentin has also been found to modulate calcium channels in skeletal myocytes [14], it has been hypothesized that this may be the pathway in which Gabapentin-induced myositis and rhabdomyolysis develops, but the exact etiology and pathogenesis is not well understood at this time [7]. Given the rarity of this diagnostic entity, the demographics also remain poorly delineated. It does not, however, appear that drug-induced myositis and rhabdomyolysis has a specific age or gender predilection.

Clinical & Imaging findings:

Rhabdomyolysis reflects the breakdown of muscle, which subsequently releases myoglobin, phosphate, potassium, urate, and creatine kinase. Rhabdomyolysis is most often a clinical diagnosis, with its main features being muscle pain, weakness, tenderness, swelling, and red-brown tinged urine in the setting of grossly elevated serum creatine kinase levels and/or impaired renal function [15].

Drug-induced myositis and rhabdomyolysis, particularly when unilateral, is considered a diagnosis of exclusion, whereby more common entities such as trauma, infection, and vascular occlusion must be ruled out. As demonstrated in this case report, Doppler ultrasound and CTA are often used as the initial diagnostic imaging modalities to rule out vascular thrombosis, hemorrhage, or an overt infectious etiology. In more diagnostically challenging cases, MRI can be of utility to definitively diagnose myopathy or myositis. As seen in this case, MRI's superior soft tissue characterization allowed for diagnosis of an inflammatory process (myositis) and delineated the extent of pathologic involvement (Fig. 8).

MRI revealed diffuse multi-compartmental hyperintense T2 signal (muscle edema) and heterogeneous contrast enhancement within the left medial thigh. Given the absence of trauma and a negative ultrasound and CTA, these MRI findings were strongly favoured to be secondary to an inflammatory process. Moreover, the recent increase of the patient's Gabapentin dose prior to admission was considered a possible inciting factor. After fluid resuscitation and cessation of Gabapentin, there was rapid improvement and resolution of the rhabdomyolysis and clinical symptoms, thus confirming the imaging diagnosis of Gabapentin-induced myositis and rhabdomyolysis.

It is unclear as to why this patient presented with unilateral symptoms and this unusual clinical presentation therefore required the use of multiple imaging modalities to reach a diagnosis, including MRI. Nevertheless, myositis is a rare, but recognized, adverse effect of Gabapentin use and this case report illustrates the radiologic findings which support a final diagnosis of Gabapentin-induced myositis.

Treatment & Prognosis:

The definitive treatment for Gabapentin-induced myositis is drug cessation and treatment of concomitant rhabdomyolysis with aggressive intravenous fluid resuscitation. Moreover, many patients will undergo other supportive therapies, such as correction of electrolyte imbalances. Serial physical exams are required to monitor for end-organ damage (ie: renal failure) or compartment syndrome along with serial laboratory studies to monitor serum electrolytes and ensure resolution of elevated creatine kinase levels. The prognosis of myositis and rhabdomyolysis greatly depends on the underlying etiology as well as the patient's comorbidities. Nevertheless, if a diagnosis is made promptly with early initiation of treatment, the prognosis remains very favorable. Moreover, the vast majority of patients have been shown to recover full baseline renal function if initially presenting with an acute kidney injury.

Differential Diagnosis:

This healthy 31 year old female presented with unilateral leg pain, weakness, and swelling, which would include a differential diagnosis that is greatly dependent upon clinical exam findings and laboratory results. Given that myositis would be considered a diagnosis of exclusion, the most critical differential diagnoses to initially rule out would include:

Muscle Ischemia

Prolonged oxygen deprivation will incite muscle ischemia and rhabdomyolysis. This would include entities such as compartment syndrome and vascular (arterial or venous) thrombosis or embolus. Compartment syndrome can be ruled out clinically, but vascular etiologies are generally assessed through the utilization of Doppler ultrasound or CTA, as seen in this case report.

Infection

Numerous bacterial, viral and fungal organisms can lead to muscular infection and rhabdomyolysis. Again, this would often be evident clinically, with the patient presenting with fever, leukocytosis or a history of immunodeficiency. In the setting of an erythematous and warm extremity, ultrasound may be of utility to look for intramuscular or subcutaneous abscess formation.

Trauma

In nearly all cases, a history of trauma would be provided or evident on clinical examination. Important mechanisms of trauma that lead to rhabdomyolysis include: direct blow trauma, crush injury, electrocution, or high degree skin burns.

TEACHING POINT

Myositis is a rare, but recognized, adverse effect of Gabapentin use. In the correct clinical setting, MRI should be recommended and drug-induced etiologies of myositis should be a diagnostic consideration for radiologists, particularly in the absence of infection or trauma.

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FIGURES

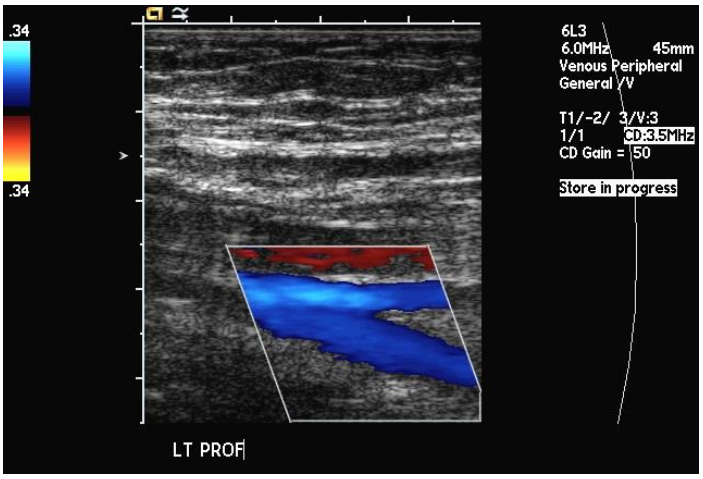

Figure 1: 31 year old female with Gabapentin-induced myositis.
Findings: Representative Doppler ultrasound image at the level of the left profundus femoris vein demonstrates normal laminar flow through the venous and arterial structures with diffuse areas of hypoechogenicity in the subcutaneous tissues of the left medial thigh.
Technique: Doppler ultrasound of the left lower extremity with use of a 6.0 MHz linear probe.

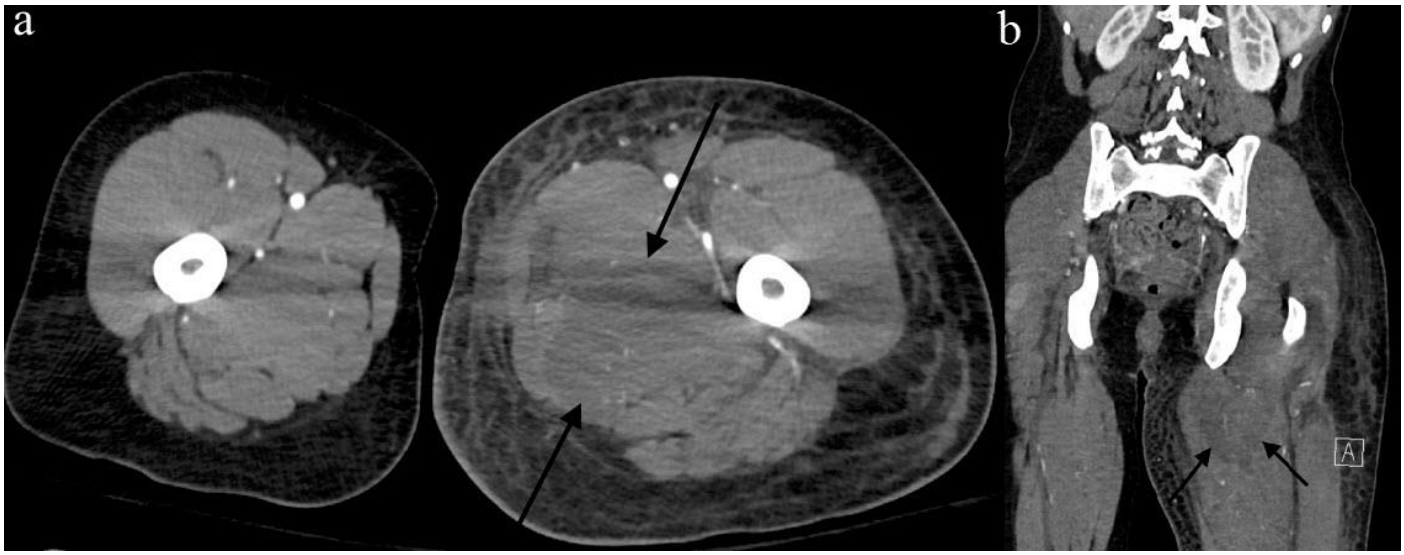

Figure 2: 31 year old female with Gabapentin-induced myositis.
Findings: Axial (a) and coronal (b) images demonstrate increased circumference of the left leg with associated subcutaneous tissue edema and a large hypoattenuating lesion (arrows) involving the adductor compartment of the left medial thigh.
Technique: Intravenous contrast enhanced arterial phase CT angiogram of the bilateral legs at the level of the mid-thigh.

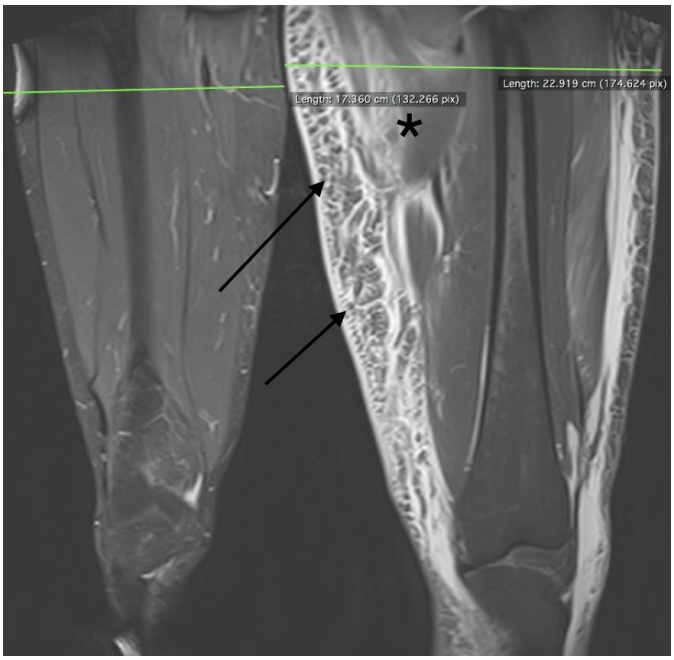

Figure 3: 31 year old female with Gabapentin-induced myositis.
Findings: Coronal image demonstrates extensive subcutaneous edema (arrows) and increased inflammatory signal within the left adductor muscles (asterisk). Measurements comparing the relative diameters of the left and right thigh are also illustrated.
Technique: Noncontrast coronal T2 Short Tau Inversion Recovery magnetic resonance imaging sequence.

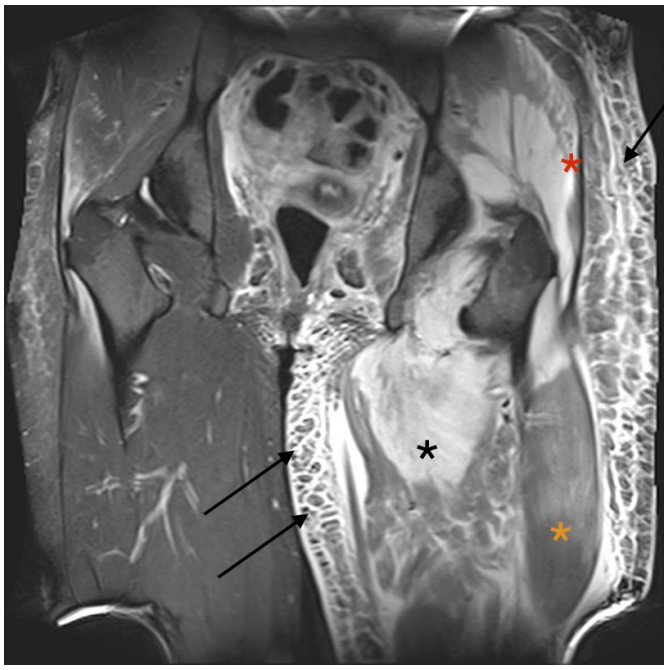

Figure 4: 31 year old female with Gabapentin-induced myositis.
Findings: Coronal image demonstrates a large hyperintense lesion within the left adductor magnus (black asterisk), left gluteus medius (red asterisk), and left vastus lateralis (orange asterisk) muscles with extensive associated subcutaneous edema (arrows).
Technique: Noncontrast coronal T2 Short Tau Inversion Recovery magnetic resonance imaging sequence.

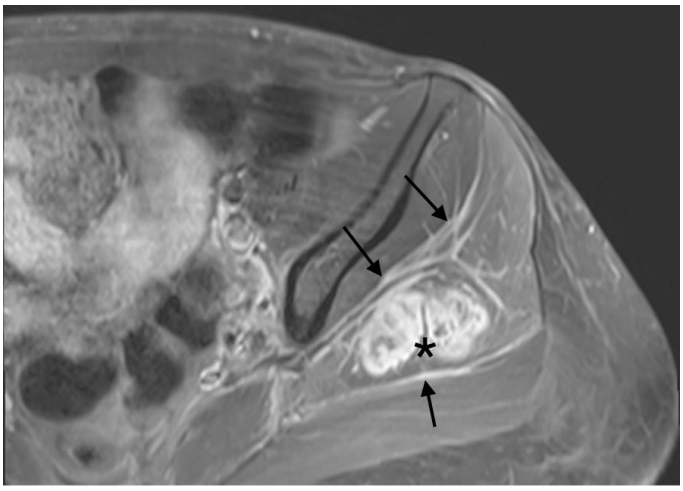

Figure 5: 31 year old female with Gabapentin-induced myositis.
Findings: Axial fat suppressed image illustrates tracking of edema between the muscle compartments (arrows) and heterogeneous increased signal, predominantly within the left gluteus medius muscle (black asterisk), most compatible with inflammatory changes.
Technique: Noncontrast axial T2 Short Tau Inversion Recovery magnetic resonance imaging sequence.

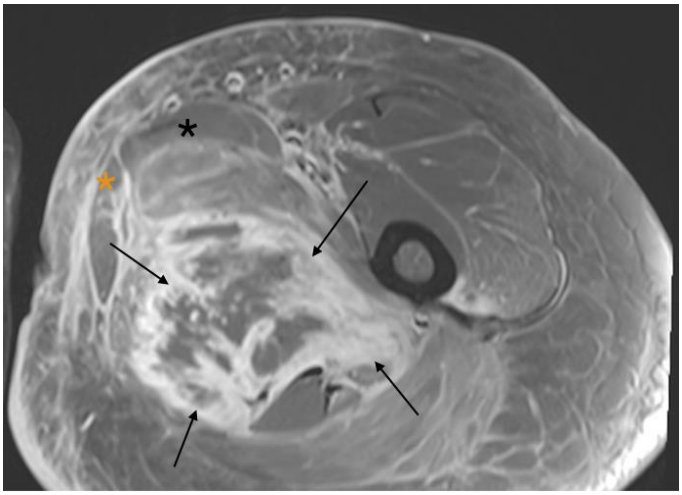

Figure 6: 31 year old female with Gabapentin-induced myositis.
Findings: Axial contrast enhanced image demonstrates areas of heterogeneous enhancement in the left adductor magnus muscle (arrows). Note is also made of inflammatory changes within the left adductor longus (black asterisk) and left gracilis (orange asterisk) muscles.
Technique: Axial fat suppressed T1 magnetic resonance imaging sequence.

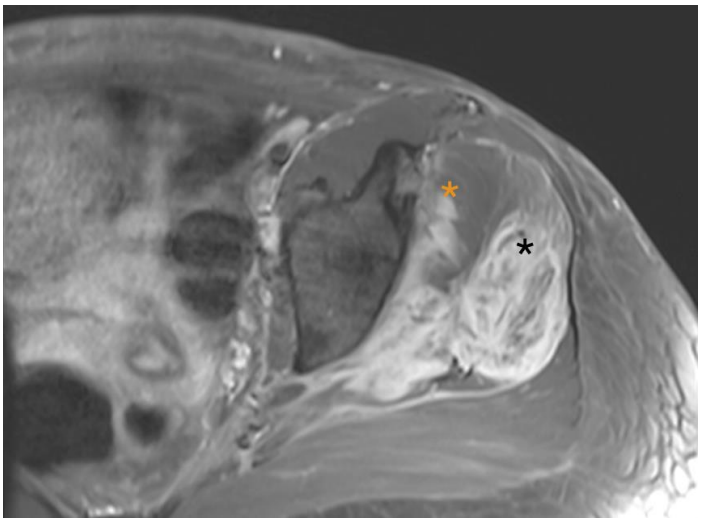

Figure 7: 31 year old female with Gabapentin-induced myositis.
Findings: Axial contrast enhanced image again demonstrates areas of inflammation and heterogeneous enhancement within the left gluteus medius (black asterisk) and left gluteus minimus (orange asterisk) muscles.
Technique: Axial fat suppressed T1 magnetic resonance imaging sequence.

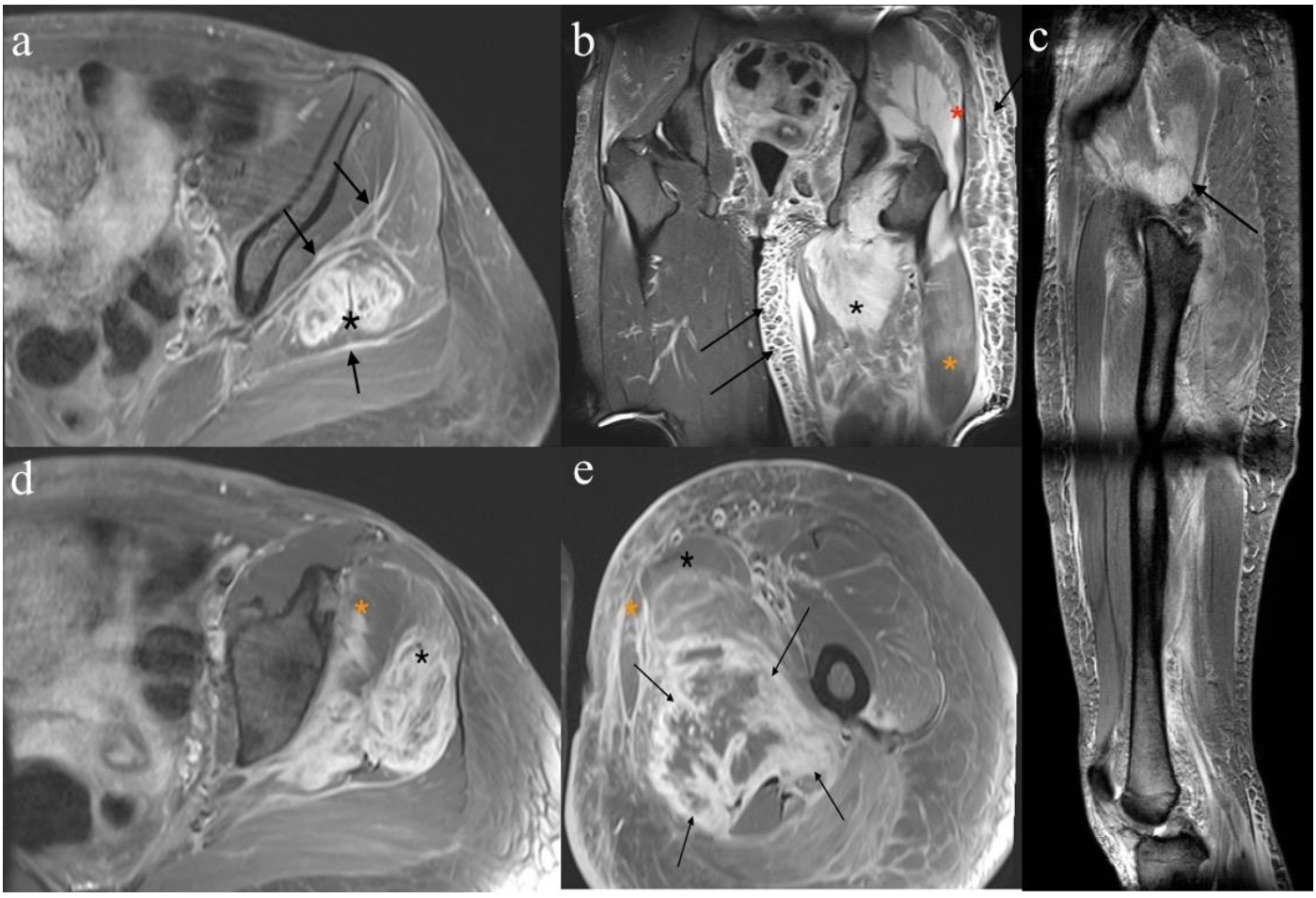

Figure 8: 31 year old female with Gabapentin-induced myositis.
Findings: Multiplanar noncontrast images demonstrate significant T2 hyperintensity involving the left gluteus medius (black asterisk - a ; red asterisk - b ; arrow - c), adductor magnus (black asterisk - b) and vastus lateralis (orange astrerisk - b) muscles along with fluid tracking between the muscle compartments (arrows - a) and extensive subcutaneous edema (arrows - b). Axial contrast enhanced images demonstrate heterogeneous enhancement of the left gluteus medius (black asterisk - d), gluteus minimus (orange asterisk - d) and adductor magnus muscles (arrows - e) as well as inflammatory changes involving the left adductor longus (black asterisk - e) and gracilis muscles (orange asterisk - e).
Technique: Noncontrast axial (a), coronal (b) and sagittal (c) T2 Short Tau Inversion Recovery and axial contrast enhanced fat suppressed T1 (d,e) magnetic resonance imaging sequences.

	Myositis	Muscle Ischemia	Infection	Trauma
History and Clinical Exam	• Often a diagnosis of exclusion. • Should be considered in the absence of history, physical exam, and laboratory findings more compatible with ischemic, infectious, or traumatic etiologies.	• Cold, pale, pulseless extremity.	• Risk factors such as overlying cellulitis, infected insect bites, injection of intravenous drugs, immunodeficiency, or diabetes. • Patients often present with fever and leukocytosis.	• History and clinical findings compatible with a direct blow trauma mechanism (i.e.: motor vehicle accident or crush injury), electrocution, or high degree skin burns.
Radiograph	• No specific findings.	• No specific findings.	• No specific findings of isolated skeletal muscle infection.	• Associated traumatic injuries, such as: acute bony fractures, pneumothoraces, hemothoraces, or large intramuscular/subcutaneous hematomas.
Ultrasound	• Muscle enlargement • +/- heterogeneous echogenicity.	• May demonstrate thrombotic or embolic vascular occlusion. • Involved muscle may be enlarged and heterogeneous in echogenicity.	• Muscle enlargement +/- abscess formation.	• Affected muscles may be enlarged. • Hematoma may demonstrate low internal echogenicity and can appear similar to a cystic mass.
Computed Tomography (CT)	• Heterogeneously hypodense appearance of the involved musculature. • In some cases, heterogeneous post-contrast enhancement.	• Severely attenuated or absent vascular contrast opacification.	• Muscle enlargement and hypoattenuation. • Effacement and stranding of surrounding fat planes. • In the setting of abscess formation: discrete intramuscular fluid collection with peripheral or rim enhancement.	• Evidence of other traumatic injuries will often be present. • Acute hemorrhage or hematoma will be of high attenuation and may demonstrate a fluid-fluid level.
Magnetic Resonance Imaging (MRI)	• Diffusely hyperintense on fluid sensitive sequences. • Iso- to hyperintense on T1-weighted imaging. • Heterogeneous or avid contrast enhancement.	• Diffuse muscle edema (hyperintense on fluid sensitive sequences) that anatomically correlates with the occluded or pathologic vessel in question.	• Diffuse muscle edema (hyperintense on fluid sensitive sequences) and muscle enlargement.	• Hematoma signal intensity will vary depending on the age of hemorrhagic products. • Acute hematoma (6 to 72 hours) will be isointense or slightly hypointense to muscle on T1 and hyperintense on T2 fluid sensitive sequences. • A hematoma will often have well demarcated margins.

Table 1: Differential diagnosis table for skeletal muscle edema and rhabdomyolysis.

Etiology	It has been hypothesized that Gabapentin's modulation of calcium channels in skeletal myocytes may be the pathway in which Gabapentin-induced myositis and rhabdomyolysis develops. Nevertheless, the exact pathogenesis of this entity is not well understood at this time.
Incidence	Rare. To our knowledge, there have only been six reported cases in the current literature.
Gender ratio	No known predilection.
Age predilection	No known predilection.
Risk factors	Gabapentin use.
Treatment	Gabapentin cessation and intravenous fluid resuscitation for concomitant rhabdomyolysis. Serial physical exams to monitor for complications and serial laboratory studies to ensure resolution of elevated creatine kinase levels.
Prognosis	Prognosis is variable depending on the etiology and the patient's comorbidities. There is a very favourable prognosis if a prompt diagnosis is made with early treatment initiation.

Table 2: Summary table for Gabapentin-induced myositis.

ABBREVIATIONS

CT - computed tomography
CTA - computed tomography angiogram
ED - emergency department
FS - fat suppressed
MRI - magnetic resonance imaging

KEYWORDS

Gabapentin; Drug-Induced; Myositis; Myopathy; Rhabdomyolysis; Computed Tomography; CT; Magnetic Resonance Imaging; MRI; Musculoskeletal; MSK; Case Report

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