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Nontraumatic Myositis Ossificans After Spontaneous Subarachnoid Hemorrhage: A Case Report

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HIGHLIGHTS

- Myositis ossificans can occur following severe brain injury.
- Computed tomography can reveal a faint 'string sign' and help early detection.
- Indomethacin can be an effective treatment for myositis ossificans.

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Nontraumatic Myositis Ossificans After Spontaneous Subarachnoid Hemorrhage: A Case Report

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Myositis ossificans is uncommon in patients with nontraumatic brain injuries. This report presents a challenging case in which myositis ossificans was diagnosed and treated by medical management in a patient who was unable to complain of any symptoms due to akinetic mutism that occurred after nontraumatic subarachnoid hemorrhage. The patient had intermittent high-grade fever, and laboratory tests showed elevated C-reactive protein and D-dimer levels without clinical signs of infection two months after subarachnoid hemorrhage. Lower-extremity venography using computed tomography was performed to rule out deep venous thrombosis. There was no thrombus, but right vastus medialis muscle showed inflammatory change with faint multilayered curvilinear hyperdense rims. The administration of indomethacin helped prevent abnormal bone formation. For the early detection of myositis ossificans, careful observation of clinical presentation and a high index of clinical suspicion is necessary in brain-injured patients. Further, elevated serum inflammatory markers accompanied by elevated alkaline phosphatase can be a critical clue. Early computed tomography helps identify early 'string sign' prior to characteristic ossification. Our report highlights that the myositis ossificans is remediable by early detection and appropriate nonsurgical management.

Keywords: Subarachnoid Hemorrhage; Myositis Ossificans; Indomethacin

INTRODUCTION

Myositis ossificans can occur following brain injury [1]. Regarding the development of myositis ossificans in association with brain injury, the most common cause is traumatic brain injury [1,2], but it can also be rarely found in patients with nontraumatic brain injury, such as stroke or hypoxic brain injury [3].

Clinical manifestations of myositis ossificans are pain, swelling, tenderness, and warmth in affected muscles. Serum alkaline phosphatase (ALP) and C-reactive protein (CRP) are early laboratory biomarkers; however, those markers are not specific for myositis ossificans [4]. Strong clinical suspicions and imaging studies, such as computed tomography (CT) and bone scintigraphy, are essential for the early detection of myositis ossificans [4,5].

Author Contributions

Conceptualization: Kim Y; Data curation: Park E, Park J, Chang SY; Formal analysis: Park E, Park J, Chang SY; Writing - original draft: Park E; Writing - review & editing: Kim Y.

This report presents a challenging case in which myositis ossificans was diagnosed and managed medically in a patient who was unable to communicate any symptoms due to akinetic mutism following nontraumatic subarachnoid hemorrhage. The clinical management of this case highlights the importance of early identification of the 'string sign,' a characteristic CT scan finding in myositis ossificans, for prompt diagnosis and suggests the potential efficacy of oral indomethacin treatment in patients with nontraumatic myositis ossificans.

CASE DESCRIPTION

A 61-year-old man had a spontaneous subarachnoid hemorrhage by a ruptured anterior communicating artery aneurysm and underwent an aneurysm clipping with craniotomy. He was admitted to our institution for inpatient rehabilitation one month later. He manifested akinetic mutism and could not communicate or complain of pain. He was confined to bed and did not show any goal-directed movement. He was completely dependent on his caregiver for all activities of daily living, with a modified Barthel index score of 0 out of 100. After 2 months, he suffered intermittent high-grade fever, and laboratory tests showed elevated CRP, procalcitonin, and D-dimer levels without clinical signs of infection. White blood cell count and proportion of segmented neutrophils were within normal range by the complete blood cell count test, and no bacteria were identified in the blood culture. Serum liver function tests revealed elevated ALP and gamma-glutamyl transpeptidase.

Abdominopelvic and lower-extremity venography CT was performed to determine whether there was hepatobiliary system abnormality or deep venous thrombosis. There was no hepatobiliary disease or thrombus, but the right vastus medialis muscle showed inflammatory change with faint multilayered curvilinear hyperdense rims (**Fig. 1**, red arrowhead). The patient underwent bone scintigraphy that revealed profound radiotracer uptake in the right vastus medialis muscle and minimal uptake in the left (**Fig. 1**, green arrowhead). At this time, the medical staff found only slight warmth, swelling, and mild stiffness in the corresponding area, and no limitation of range of motion was noted.

With the diagnosis of myositis ossificans, we thoroughly monitored the possible development of a range of motion limitation and provided conventional physical therapy to enhance mobility and prevent joint contracture. The indomethacin was administered per os with a dose of 25mg three times daily for four weeks. Two months after medical management, body temperature and the results of blood tests, including CRP and liver function tests, showed gradual improvement (**Figs. 2** and **3**, **Table 1**). The follow-up bone scintigraphy and plan X-ray demonstrated the resolution of myositis ossificans (**Fig. 1**, green arrowhead and black arrows).

DISCUSSION

Early detection of myositis ossificans can be challenging in patients with severe brain injury. Severe brain injuries often accompany decreased consciousness or profound cognitive impairments, so symptoms and signs of myositis ossificans can be discovered late. In particular, our patient had ischemic damage to the bilateral cingulate gyrus due to vasospasm following the rupture of the anterior communicating artery aneurysm and showed clinical manifestations of akinetic mutism. Akinetic mutism is a neurologic condition in which consciousness and sensorimotor capacity are preserved, but clinical features such as apathy

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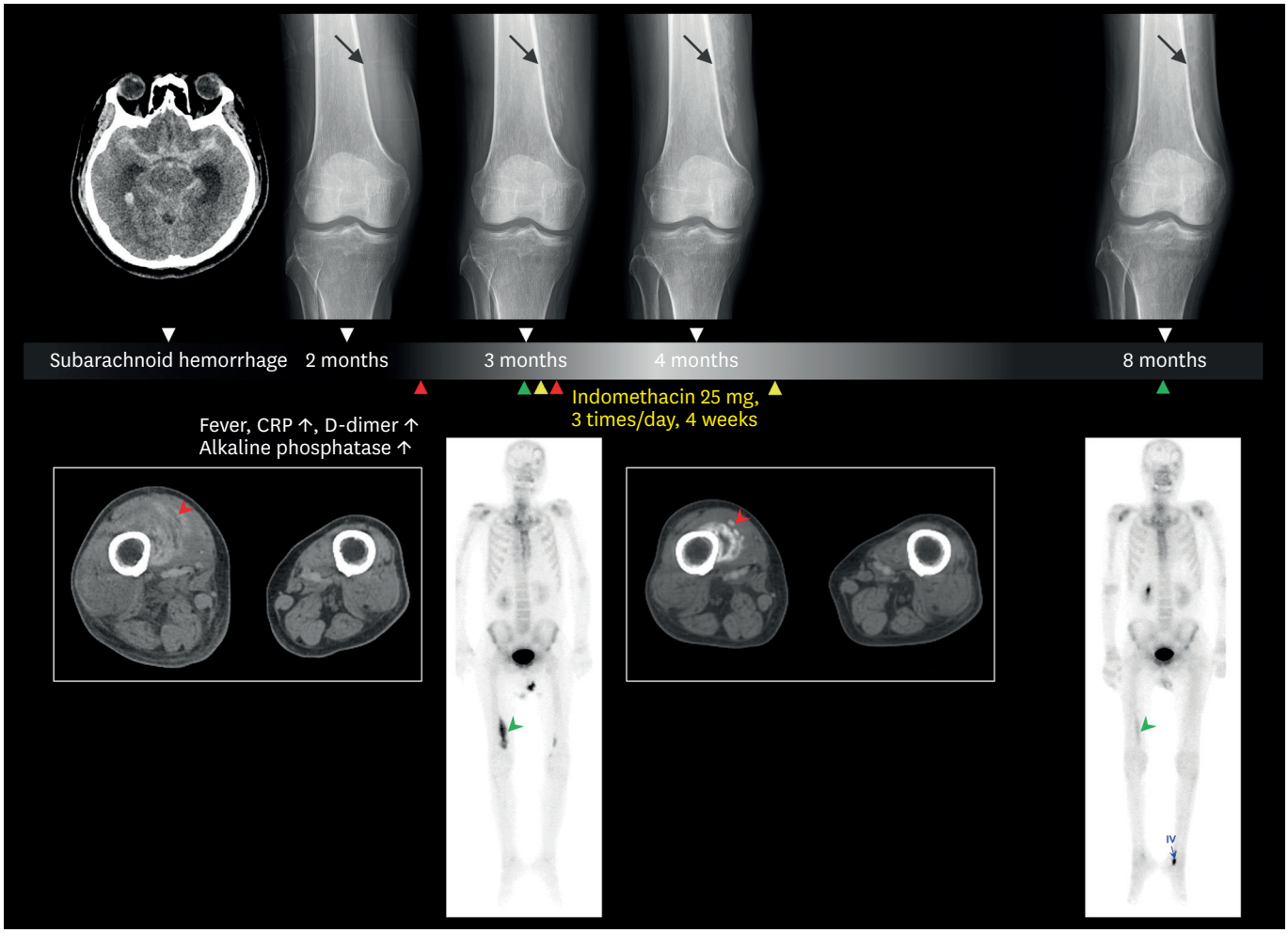

Fig. 1. Clinical course and serial multimodal imaging findings of myositis ossificans. Four serial X-rays show soft tissue swelling and faint, apparent, and fading radiopaque lesions in the right vastus medialis muscle, respectively (black arrows). Two serial computed tomography reveals faint multilayered curvilinear hyperdense rims, suggesting the early phase of myositis ossificans, and circumferential calcification with a radiolucent center, suggesting the maturing ossification (red arrowheads). Two serial bone scintigraphy shows increased uptake in the early phase and decreased uptake after indomethacin treatment (green arrowheads).

and indifference to pain may be present. The patient could not complain of pain, and the warmth or stiffness of the affected muscles was not prominent, making it difficult to suspect myositis ossificans. Our patient had elevated D-dimer, and lower-extremity venography CT was performed to differentiate deep vein thrombosis. Early CT scan, revealing faint multilayered curvilinear hyperdense rims, played a pivotal role in the diagnostic progress for myositis ossificans. The subsequent bone scan confirmed myositis ossificans involving the bilateral vastus medialis muscles, and recovery was achieved with indomethacin administration.

Several serum markers, including ALP and CRP, can aid in the early detection of myositis ossificans. However, their diagnostic values are limited because they are not specific for myositis ossificans [4,6]. Serum ALP, a marker indicative of osteoblast activity, can remain within normal ranges during the initial phase of myositis ossificans. A marked increase can be observed approximately three weeks post-onset, concurrent with ossification, and those levels peak around the 10th week [4]. Inflammatory markers, including CRP,

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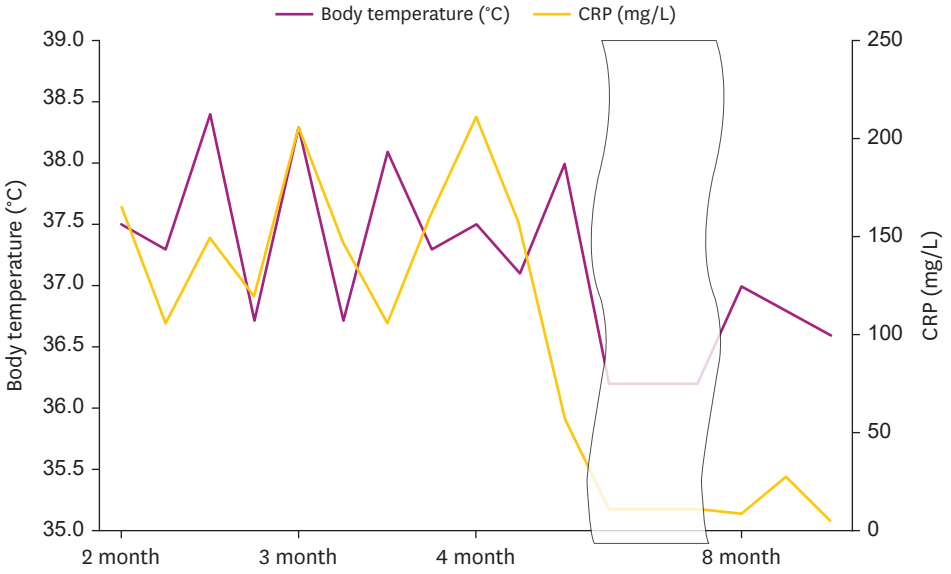

Fig. 2. As the myositis ossificans occurred two months after subarachnoid hemorrhage, the body temperature was elevated, and the CRP fluctuated following changes in body temperature. After the myositis ossificans was resolved, the body temperature and CRP were normalized.
CRP, C-reactive protein.

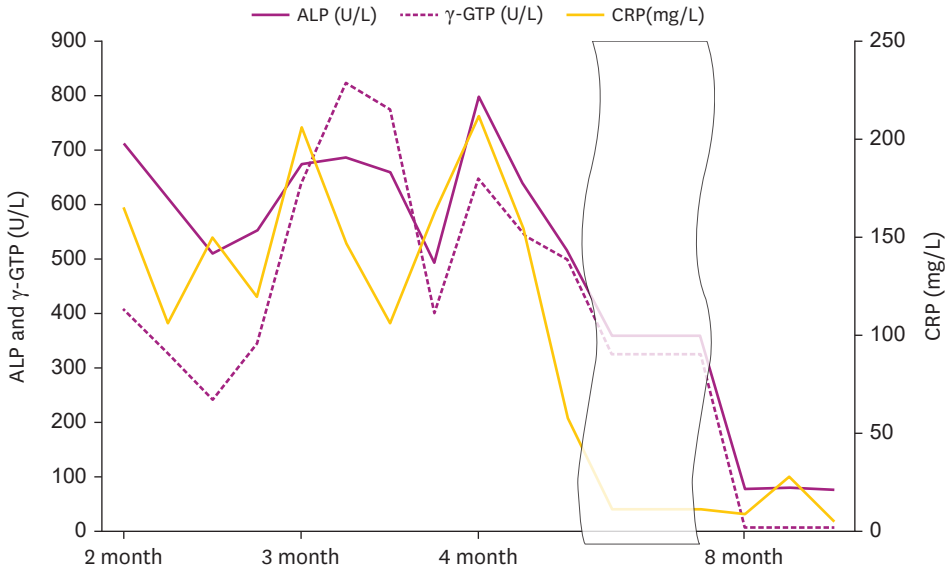

Fig. 3. The ALP and γ-GTP were elevated simultaneously as the myositis ossificans occurred, and this trend was linked to changes in CRP level. After myositis ossificans improved, the ALP and γ-GTP were normalized.
ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transferase; CRP, C-reactive protein.

Table 1. Linked changes in body temperature, CRP, ALP, and γ-GTP

Biomarkers	2 month				3 month				4 month				8 month		
	Week				Week				Week				Week		
	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd
Body temp (°C)	37.5	37.3	38.4	36.7	38.3	36.7	38.1	37.3	37.5	37.1	38.0	36.2	37.0	36.8	36.6
CRP (mg/dL)	165	105	149	119	206	147	105	162	211	155	58	11	8	27	5.25
ALP (U/L)	713	610	510	552	674	687	660	491	798	638	516	359	77	80	76
γ-GTP (U/L)	407	326	240	345	637	823	775	401	648	546	499	325	6	7	7

CRP, C-reactive protein; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transferase.

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erythrocyte sedimentation rate, and prostaglandin-E2, can be documented in the early stage of myositis ossificans [4]. Creatine phosphokinase can also be elevated in conjunction with the progression of inflammation or ossification in the affected muscles [4,7]. The patient had a persistent elevation of serum ALP and γ-glutamyl transferase (γ-GTP). However, creatine phosphokinase level was within normal range, which did not corroborate muscle inflammation or damage [4]. Furthermore, γ-GTP was not previously known as a biomarker for myositis ossificans; those laboratory findings required differential diagnosis for hepatobiliary pathologic conditions. The patient also had elevated CRP and D-dimer levels over two to three months, suggesting an ongoing inflammatory process. However, there has been no established evidence providing the link between the D-dimer elevation and myositis ossificans, so those inflammatory markers could not serve as distinct diagnostic clues. While elevated serum markers in our patient, including serum ALP, γ-GTP, CRP, and D-dimer, might be related to the development of myositis ossificans, further accumulation of evidence will be warranted to determine the association between elevations of various serum markers and myositis ossificans.

The CT findings played a crucial role in the early detection of myositis ossificans. CT scan is a gold standard for identifying early characteristic findings of myositis ossificans, which include extensive muscle and perilesional edema without accompanying bone marrow or cortical abnormalities [4,8]. Early CT scan can also delineate the lesion that is demarcated from the cortex of the adjacent bone by a radiolucent cleft, known as the 'string sign.' The 'string sign' typically becomes evident on the CT approximately 4–6 weeks [9]. In our case, the first CT scan, showing the inflammatory change with faint multilayered curvilinear hyperdense rims, helped diagnose the myositis ossificans prior to the characteristic circumferential calcification with a radiolucent center shown in the second CT scan. Serial CT scans may be beneficial for detecting and tracking of changes across the clinical course of myositis ossificans [10]. Other imaging studies, such as ultrasonography, bone scintigraphy, and magnetic resonance imaging, also help diagnose myositis ossificans. Bone scintigraphy can reveal increased uptake in the early stage of myositis ossificans before mineralization, which is apparent on plain radiographs, which show calcification within 2–6 weeks after the onset of symptoms [11]. Radionuclide uptake can persist 6 to 18 months after initial detection [5]. Our patient demonstrated the resolution of radionuclide uptake six months post-detection by first bone scintigraphy. Longitudinal assessment using bone scintigraphy was helpful in monitoring the clinical course and treatment efficacy.

The pathological mechanism underlying the formation of myositis ossificans is less understood yet [12,13]. The most explanatory mechanism for the development of myositis ossificans is a local inflammatory cascade occurring after skeletal muscle injury, which leads to the release of cytokines that differentiate endothelial-mesenchymal stem cells within the skeletal muscle into chondrocytes or osteoblasts, resulting in myositis ossificans formation [4]. While 75% of myositis ossificans cases are known to occur as a result of trauma, the remaining 25% of cases can also occur in nontraumatic situations [13]. Nontraumatic myositis ossificans can occur in periarticular muscles following brain injury, and immobilization is known as a significant risk factor [14]. The prevalence of heterotopic ossification in stroke is about 0.5%–1.3% [1,15], but myositis ossificans, a subtype of heterotopic ossification, is estimated to be lower. The pathophysiology of heterotopic ossification in nontraumatic brain injury is presumed to be induced by disturbances of the autonomic nervous system or robust inflammatory response [1], but the precise mechanism remains unclear.

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Our patient demonstrated the resolution of myositis ossificans by administering indomethacin for 4 weeks. Cyclooxygenase enzymes are involved in the inflammatory process by converting arachidonic acid into prostaglandins, which are compounds that contribute to inflammation, pain, and fever. Nonsteroidal anti-inflammatory drugs exert their therapeutic effects by inhibiting the cyclooxygenase enzymes, reducing prostaglandin synthesis. Prostaglandins have been recognized as contributors to the abnormal bone formation seen in myositis ossificans, possibly by stimulating osteoblast activity [2]. Consequently, nonsteroidal anti-inflammatory drugs, through the suppression of prostaglandin production and direct suppression of osteoblast cell cycle progression, may inhibit ectopic bone growth.

In the early stage of myositis ossificans, passive range of motion exercises are recommended to maintain joint mobility [4,8]. As the ossification matures in patients with myositis ossificans, a more active approach can be adopted with resistive strengthening exercises to improve a range of motion [4]. Surgical intervention is reserved for failed medical management, such as intractable pain, neurovascular compromise, and limitation of range of motion in the mature phase [4,10,16]. Surgery should be performed after complete maturation, and recurrence is known to occur if the myositis ossificans is excised while it is metabolically active [17].

Myositis ossificans is uncommon following nontraumatic brain injuries. For the early diagnosis of myositis ossificans, careful observation of clinical presentation, such as fever, swelling, and limited range of motion, is needed, and a high index of clinical suspicion is crucial, especially for brain-injured patients. Additionally, attention should be given to elevations in inflammatory markers such as CRP, accompanied by elevations in serum ALP. If clinical manifestations and laboratory findings suggest myositis ossificans, conducting a CT scan or bone scintigraphy can shorten the diagnostic process, leading to a favorable prognosis. Our patient was unable to communicate due to akinetic mutism, which posed challenges in the early detection of myositis ossificans. The early CT scan demonstrated inflammatory change with faint multilayered curvilinear hyperdense rims and played an important role in diagnosing myositis ossificans prior to characteristic ossification. The administration of anti-inflammatory medication helped prevent abnormal bone formation. Our report highlights that early detection can be made based on the characteristic findings of CT scan, and this condition is remediable by appropriate nonsurgical management.

REFERENCES

1. Cunha DA, Camargos S, Passos VM, Mello CM, Vaz LS, Lima LR. Heterotopic ossification after stroke: clinical profile and severity of ossification. J Stroke Cerebrovasc Dis 2019;28:513-520. PUBMED | CROSSREF
2. Ranganathan K, Loder S, Agarwal S, Wong VW, Forsberg J, Davis TA, Wang S, James AW, Levi B. Heterotopic ossification: basic-science principles and clinical correlates. J Bone Joint Surg Am 2015;97:1101-1111. PUBMED | CROSSREF
3. Kluger G, Kochs A, Holthausen H. Heterotopic ossification in childhood and adolescence. J Child Neurol 2000;15:406-413. PUBMED | CROSSREF
4. Walczak BE, Johnson CN, Howe BM. Myositis ossificans. J Am Acad Orthop Surg 2015;23:612-622. PUBMED | CROSSREF
5. Tyler P, Saifuddin A. The imaging of myositis ossificans. Semin Musculoskelet Radiol 2010;14:201-216. PUBMED | CROSSREF
6. Dong L, Dong G, Cao J, Zhang J. Association of α2-HS glycoprotein with neurogenic heterotopic ossification in patients with spinal cord injury. Med Sci Monit 2017;23:5382-5388. PUBMED | CROSSREF

7. Singh RS, Craig MC, Katholi CR, Jackson AB, Mountz JM. The predictive value of creatine phosphokinase and alkaline phosphatase in identification of heterotopic ossification in patients after spinal cord injury. Arch Phys Med Rehabil 2003;84:1584-1588. PUBMED | CROSSREF
8. Shehab D, Elgazzar AH, Collier BD. Heterotopic ossification. J Nucl Med 2002;43:346-353. PUBMED
9. Aneiros-Fernandez J, Caba-Molina M, Arias-Santiago S, Ovalle F, Hernandez-Cortes P, Aneiros-Cachaza J. Myositis ossificans circumscripta without history of trauma. J Clin Med Res 2010;2:142-144. PUBMED | CROSSREF
10. Mujtaba B, Taher A, Fiala MJ, Nassar S, Madewell JE, Hanafy AK, Aslam R. Heterotopic ossification: radiological and pathological review. Radiol Oncol 2019;53:275-284. PUBMED | CROSSREF
11. Kransdorf MJ, Meis JM, Jelinek JS. Myositis ossificans: MR appearance with radiologic-pathologic correlation. AJR Am J Roentgenol 1991;157:1243-1248. PUBMED | CROSSREF
12. Kaplan FS, Glaser DL, Hebela N, Shore EM. Heterotopic ossification. J Am Acad Orthop Surg 2004;12:116-125. PUBMED | CROSSREF
13. El Bardouni A, Boufettal M, Zouaidia F, Kharmaz M, Berrada MS, Mahassini N, El Yaacoubi M. Non-traumatic myositis ossificans circumscripta: a diagnosis trap. J Clin Orthop Trauma 2014;5:261-265. PUBMED | CROSSREF
14. Alexander KA, Tseng HW, Salga M, Genêt F, Levesque JP. When the nervous system turns skeletal muscles into bones: how to solve the conundrum of neurogenic heterotopic ossification. Curr Osteoporos Rep 2020;18:666-676. PUBMED | CROSSREF
15. Chua KS, Kong KH. Acquired heterotopic ossification in the settings of cerebral anoxia and alternative therapy: two cases. Brain Inj 2003;17:535-544. PUBMED | CROSSREF
16. Mahale YJ, Vyawahare CS, Dravid NV, Upase A, Rathi R. A rare case of non traumatic myositis ossificans circumscripta. J Orthop Case Rep 2015;5:15-17. PUBMED | CROSSREF
17. Saussez S, Blaivie C, Lemort M, Chantrain G. Non-traumatic myositis ossificans in the paraspinal muscles. Eur Arch Otorhinolaryngol 2006;263:331-335. PUBMED | CROSSREF