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Intercostal Heterotopic Ossification: A Rare Cadaveric Case Study with Multimodal Analysis

Osificación Heterotópica Intercostal: Un Estudio de Caso Cadavérico poco Frecuente con Análisis Multimodal

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SUMMARY: Heterotopic ossification (HO) is a pathological condition characterized by ectopic bone formation in soft tissues. This study presents a rare case of anterior intercostal HO discovered in a 62-year-old Korean male cadaver during an educational dissection. The HO structure, which connected multiple ribs, underwent radiological examination (X-ray and CT scans) and histological analysis. Radiographic findings revealed that mature bone had formed adjacent to the ribs, surrounded by fibrous tissue. Histological analysis demonstrated a progression from fibrous tissue to mature bone, indicative of endochondral ossification, with no proliferative activity detected in the Ki-67 immunostaining. This case provides valuable insights into intercostal HO's morphological, radiological, and histological characteristics, providing significant information in anatomy and pathology for educational purposes.

KEY WORDS: Anterior intercostal; Cadaver; CT scan; Heterotopic ossification; X-ray.

INTRODUCTION

Heterotopic ossification (HO) is a pathological process characterized by the formation of extraskeletal bone in soft tissues (Meyers *et al*., 2019). The etiology of HO can be categorized into genetic factors, such as fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH), and non-genetic factors, including neurogenic, post-traumatic, post-surgical, and reactive lesions (Vanden & Vanderstraeten, 2005). HO can occur in various connective tissues, with areas adjacent to joints particularly susceptible (Ranganathan *et al*., 2015; Meyers *et al*., 2019).

While HO commonly affects muscles, fascia, tendons, and ligaments near major joints, thoracic manifestations, especially in the intercostal area, are rare (Greiffenstein *et al*., 2019; Al Khader *et al*., 2023). Anterior intercostal HO with bridging formation is particularly uncommon, contrasting with the more frequently observed posterior intercostal HO (Nuovo *et al*., 1922; Harmon & Nielsen, 1994; Koob *et al*., 2010; Van Wijck *et al*., 2023).

The pathogenesis of HO involves local injury and systemic stress, which creates a pro-inflammatory environment that stimulates heterotopic bone formation (Kim, 2018). This process typically progresses through early, intermediate, and mature phases (Walczak *et al*., 2015), following endochondral or intramembranous ossification pathways or a combination of both (Foley *et al*., 2018).

Terminology for HO often reflects the affected tissue, such as myositis ossificans (MO), for skeletal muscle involvement. However, this nomenclature can be misleading as HO is not specific to muscle (Meyers *et al*., 2019). Differential diagnosis is crucial, as HO may mimic other conditions like osteosarcoma (Greiffenstein *et al*., 2019). Accurate diagnosis relies on patient history, clinical symptoms, imaging, and histological confirmation, emphasizing invasive biopsy for definitive assessment (Harmon & Nielsen, 1994; Lacout *et al*., 2012).

This study presents a rare cadaveric case of anterior intercostal HO, providing morphological, radiological, and histological analyses. The findings contribute valuable insights to education in anatomy and pathology.

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CASE REPORT

During an educational dissection at Chonnam National University Medical School, a 62-year-old Korean male cadaver underwent a standard dissection procedure. The authors state that every effort was made to follow all local and international ethical guidelines and laws pertaining to using human cadaveric donors in anatomical research (Iwanaga *et al*., 2022). The present study was performed in accordance with the requirements of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). After removing the skin, superficial fascia, fat, and intercostal muscles, a firm bridged structure was identified in the intercostal area. The structure remained intact after excising the surrounding tissue. The bridged formations were observed between the right fourth and fifth ribs anteriorly (Rt1) (Fig. 1a), the left side, anterolaterally between the third and fourth ribs (Lt1), as well as anterolaterally between the fourth and fifth ribs (Lt2) and anteriorly between the fourth and fifth ribs (Lt3) (Fig. 1b). The structure was extracted by cutting the respective ribs for further analysis. Radiographic imaging (X-ray and CT scans) revealed that the peripheral zone near the ribs exhibited bone characteristics due to density variations. At the same time, the remaining part appeared as soft tissue (Fig. 2a, b, c). Histological analysis confirmed the soft tissue as fibrous tissue through H&E staining (Fig. 2d, e).

The extent of HO varied across the different bridged formations:

- Rt1 showed a small amount of mature bone at the superior part of the fifth rib, with mostly fibrous tissue throughout.
- Lt1 displayed more advanced HO than Rt1, extending from the superior part of the fourth rib to the middle of the bridged structure.
- Lt2 exhibited the most extensive HO, with mature bone formation throughout, except for a small central region of fibro-osteoid tissue.

H&E histology revealed a central zone of fibrous tissue, an intermediate zone with hypertrophic cells showing chondrocyte maturation and endochondral bone formation, and a peripheral zone of mature bone adjacent to the ribs (Fig. 3a, b). Immunohistochemical analysis using anti-Ki67 antibody showed no positive reactive cells, indicating an absence of proliferative activity and suggesting that the HO progression had ceased (Fig. 3c).

This rare cadaveric case report of anterior and anterolateral intercostal HO demonstrates that the ossification process occurred in the past and was arrested at varying stages of progression in different locations.

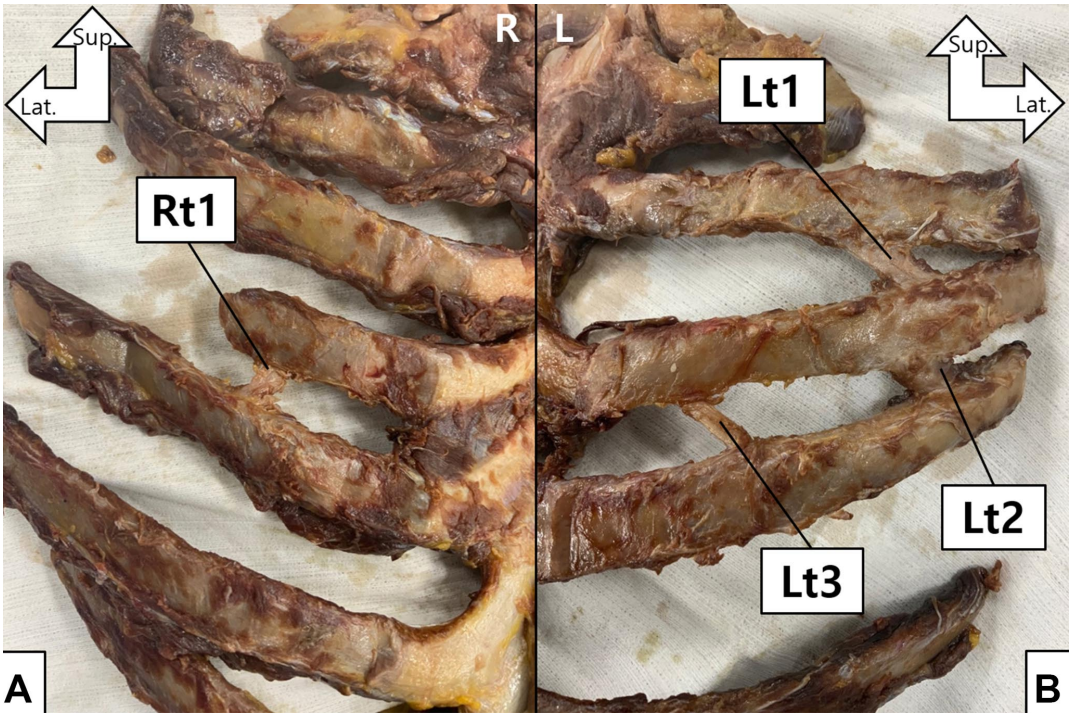

Fig. 1. The morphology of heterotopic ossification (HO). (a) Between the right fourth and fifth ribs anteriorly (Rt1), (b) between the left anterolateral third and fourth ribs (Lt1), and fourth and fifth ribs (Lt2) and anteriorly between the fourth and fifth ribs (Lt3).

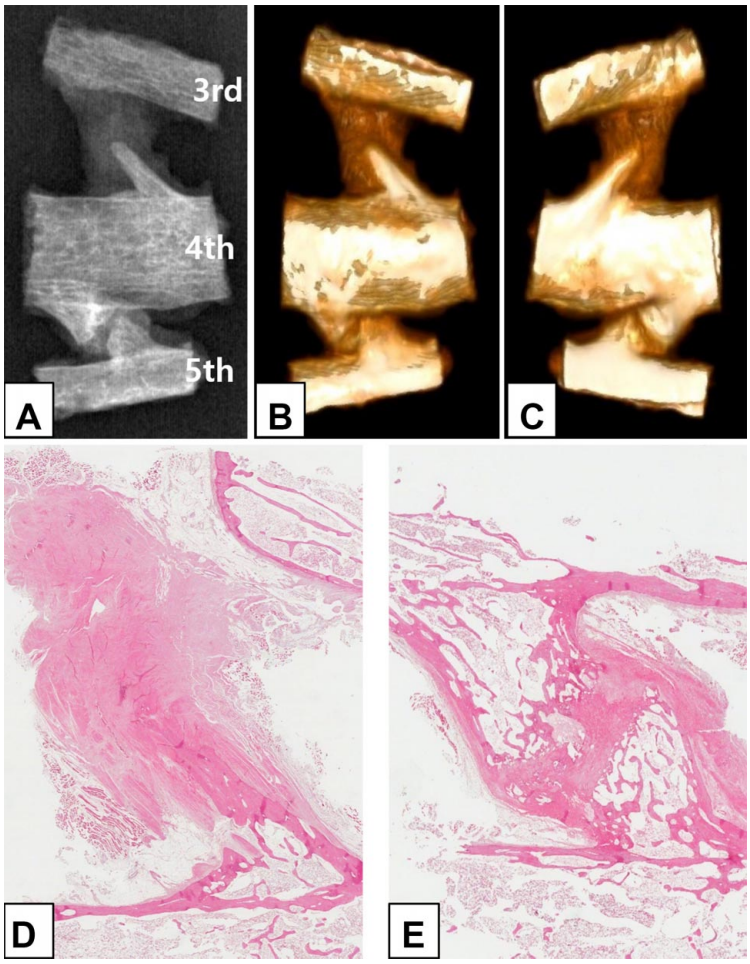

Fig. 2. (a–e) Radiographic and histological analysis of Lt1 and Lt2: (a) X-ray in the AP view, (b) CT in the AP view, and (c) CT in the PA view showed that Lt1 had mature bone extending from the superior part of the fourth rib to the middle part of the bridged structure, and Lt2 had mature bone almost in contact from the inferior part of the fourth rib to the fifth rib. (d) H&E staining of Lt1 showed that the remaining soft tissue consisted of fibrous tissue. (e) Lt2 showed that fibrous tissue was nearly absent, with the remaining part consisting of fibro-osteoid tissue.

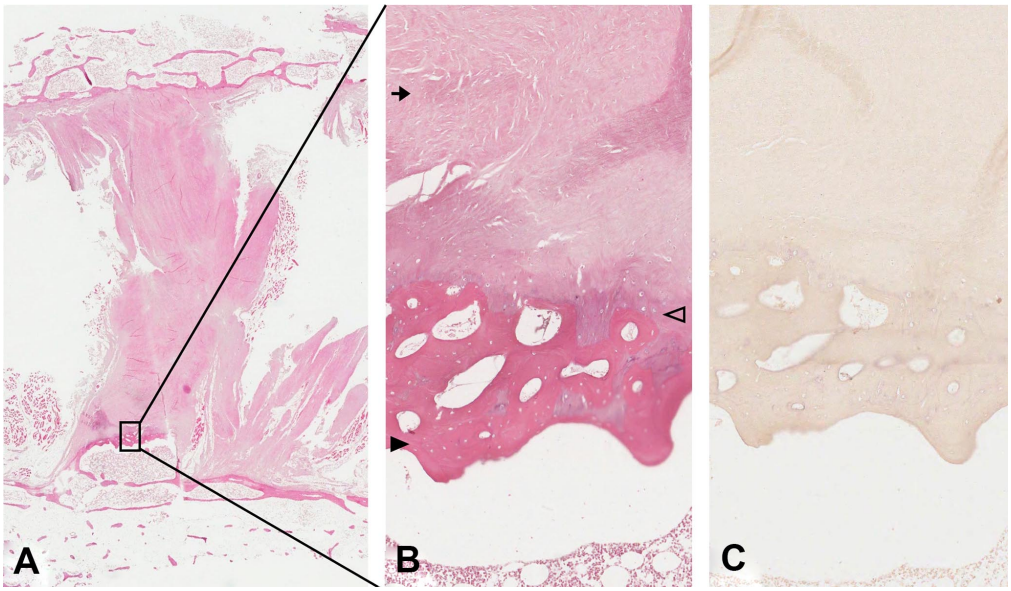

Fig. 3. (a–b) Histological appearance of Rt1 by H&E staining, (a) whole-mount of Rt1, (b) enlarged image of rectangular area shows fibrous tissue in the center area (arrow), endochondral ossification in the intermediate area (empty arrowhead), and mature bone formation in the periphery area (black arrowhead). (c) The IHC appearance of Rt 1 does not show Ki-67 immunoreactivity.

DISCUSSION

HO has both genetic and non-genetic etiologies. Rare genetic conditions like FOP and POH exhibit distinct characteristics (Vanden & Vanderstraeten, 2005). FOP typically emerges in early childhood, following specific ossification patterns throughout the body, while POH involves unpredictable intramembranous ossification (Kaplan *et al*., 2004). Non-genetic HO can arise from neurogenic factors (e.g., spinal cord injury, traumatic brain injury), trauma, or surgical procedures (Ranganathan *et al*., 2015; Saad *et al*., 2021). Our case presents a rare bridged HO formation in the anterior intercostal area, likely stemming from a traumatic incident approximately a decade before the donor's death.

The histopathological mechanism of non-genetic HO remains debated, with descriptions ranging from endochondral to intramembranous processes or a combination of both (Foley *et al*., 2018). Our research aligns with previous studies on periarticular non-genetic HO, revealing a progression from fibrous tissue to mature bone through endochondral ossification. This process typically involves six distinct stages: Perivascular lymphocytic infiltration, lymphocytic migration into soft tissue, reactive fibroproliferation, neovascularity, cartilage formation, and endochondral bone formation (Foley *et al*., 2018). In our case, the absence of Ki-67 expression suggests that the HO process was complete, with no ongoing proliferation.

MO, the most common form of HO, is often misapplied to describe HO, even when it lacks specific muscle involvement or inflammation (Walczak *et al*., 2015; Meyers *et al*., 2019; Saad *et al*., 2021). In our case, we opted for HO due to the absence of muscular inflammation. Distinguishing HO from malignant soft tissue or osteogenic sarcomas is crucial due to their vastly different prognoses and treatments (Harmon & Nielsen, 1994; Lacout *et al*., 2012). This differentiation relies heavily on the characteristic "zonation pattern" or "zone phenomenon" observed in HO (Savvidou *et al*., 2021).

Diagnosis of HO typically relies on a combination of patient history, clinical symptoms, and imaging studies. X-rays serve as the initial imaging modality, while CT scans can detect calcifications at an earlier stage (Savvidou *et al*., 2021). MRI is effective for visualizing soft-tissue masses, and ultrasound offers a low-cost method for early detection (Walczak *et al*., 2015). X-ray and CT scans were employed in our case, revealing mature bone formation adjacent to the ribs with a central fibrous tissue component. Histological confirmation through biopsy is often necessary, with careful attention paid to the characteristic zonation pattern of HO (Lacout *et al*., 2012; Patru *et al*., 2021).

Our histological analysis demonstrated a clear progression from fibrous tissue to mature bone, indicative of endochondral ossification. The central zone consisted of fibrous stroma, transitioning to an intermediate zone with hypertrophic cells showing chondrocyte maturation and finally to a peripheral zone of mature bone. This pattern stands in stark contrast to osteosarcoma, where tumor growth is centrifugal, with more mature cells concentrated in the center (Harmon & Nielsen, 1994).

The absence of proliferative activity, as evidenced by negative Ki-67 immunostaining, suggests that the HO, in our case, had reached a stable, non-progressive state. This finding holds important implications for understanding the natural history of HO and potential treatment strategies.

Interestingly, our case of anterior intercostal HO with bridged formation is extremely rare. While HO in the chest has occasionally been reported, it typically forms a mass or occurs in the posterior area (Nuovo *et al*., 1922; Harmon & Nielsen, 1994; Koob *et al*., 2010; Van Wijck *et al*., 2023). The bridging formation observed in our case could potentially interfere with respiratory function by limiting chest wall mobility (Greiffenstein *et al*., 2019; Van Wijck *et al*., 2023), similar to the effects of flail chest (Al-Qadi, 2018). However, the lack of medical treatment sought by the donor suggests that the condition may have been asymptomatic or caused minimal discomfort.

This study underscores the importance of a comprehensive understanding of HO to avoid unnecessary diagnostics and treatments. It also highlights the value of thorough anatomical, radiological, and histological examinations in accurately identifying and characterizing unusual presentations of HO. Future research could focus on the long-term progression and potential functional impacts of such rare HO formations.

Moreover, this case provides valuable insights for educational purposes in anatomy and pathology. It demonstrates the significance of considering HO in differential diagnoses, especially in cases with atypical presentations or locations. The multidisciplinary approach used in this study—combining gross anatomical observation, radiological imaging, and histological analysis—is an excellent model for comprehensively evaluating anatomical anomalies.

Our case report on anterior intercostal traumatic HO with bridged formation significantly contributes to the literature on HO. It emphasizes the importance of meticulous evaluation and accurate diagnosis of bone-forming lesions, particularly in atypical locations. As our understanding of HO evolves, cases like this provide crucial data points for enhancing diagnostic accuracy and developing targeted treatment strategies.

Ethics approval statement. The authors state that every effort was made to follow all local and international ethical guidelines and laws that pertain to the use of human cadaveric donors in anatomical research (Iwanaga *et al*. 2022). The present study was performed in accordance with the requirements of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

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HUR, S.; CHO, Y. S.; CHO, H. J.; GO, G. G. & NAM, K. I. Osificación heterotópica intercostal: un estudio de caso cadavérico poco frecuente con análisis multimodal. *Int. J. Morphol., 42(6)*:1585-1590, 2024.

RESUMEN: La osificación heterotópica (OH) es una afección patológica caracterizada por la formación de hueso ectópico en los tejidos blandos. Este estudio presenta un caso poco frecuente de osificación heterotópica intercostal anterior descubierta en un cadáver de un individuo masculino coreano de 62 años durante una disección educativa. La estructura de la osificación heterotópica, que conectaba múltiples costillas, se sometió a un examen radiológico (radiografías y tomografías computarizadas) y un análisis histológico. Los hallazgos radiográficos revelaron que se había formado hueso maduro adyacente a las costillas, rodeado de tejido fibroso. El análisis histológico demostró una progresión de tejido fibroso a hueso maduro, indicativo de osificación endocondral, sin actividad proliferativa detectada en la inmunotinción Ki-67. Este caso proporciona información valiosa sobre las características morfológicas, radiológicas e histológicas de las OH intercostales, brindando información significativa en anatomía y patología para fines educativos.

PALABRAS CLAVE: Intercostal anterior; Cadáver; Tomografía computarizada; Osificación heterotópica; Radiografía.

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