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Contents

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EDITORIAL

- 1 Impact of gut-brain interaction in emerging neurological disorders
Lin MS, Wang YC, Chen WJ, Kung WM

OPINION REVIEW

- 7 Postoperative diarrhea in Crohn's disease: Pathogenesis, diagnosis, and therapy
Wu EH, Guo Z, Zhu WM

REVIEW

- 17 Endplate role in the degenerative disc disease: A brief review
Velmar T, Gradisnik L
- 30 Challenges for clinicians treating autoimmune pancreatitis: Current perspectives
Kim SH, Lee YC, Chon HK

MINIREVIEWS

- 47 Intestinal microecology-based treatment for inflammatory bowel disease: Progress and prospects
Yan XX, Wu D
- 57 Rehabilitation care of patients with neurogenic bladder after spinal cord injury: A literature review
Xiang L, Li H, Xie QQ, Siau CS, Xie Z, Zhu MT, Zhou B, Li ZP, Wang SB
- 65 Role of natural products and intestinal flora on type 2 diabetes mellitus treatment
Aydin OC, Aydin S, Barun S
- 73 Role of the extracellular matrix in COVID-19
Huang JJ, Wang CW, Liu Y, Zhang YY, Yang NB, Yu YC, Jiang Q, Song QF, Qian GQ
- 84 Diabetic wounds and artificial intelligence: A mini-review
Tehsin S, Kausar S, Jameel A

ORIGINAL ARTICLE

Clinical and Translational Research

- 92 Identification of a four-miRNA signature predicts the prognosis of papillary thyroid cancer
Yang F, Zhou YL

Retrospective Cohort Study

- 104 Completion of 6-mo isoniazid preventive treatment among eligible under six children: A cross-sectional study, Lagos, Nigeria
Adepoju VA, Adelekan A, Agbaje A, Quaitey F, Ademola-Kay T, Udoekpo AU, Sokoya OD

Retrospective Study

- 116 Impact of central venous port implantation method and access choice on outcomes
Erdemir A, Rasa HK

CASE REPORT

- 127 Extracorporeal shock wave for plantar flexor spasticity in spinal cord injury: A case report and review of literature
Comino-Suárez N, Gómez-Soriano J, Ceruelo-Abajo S, Vargas-Baquero E, Esclarín A, Avendaño-Coy J
- 135 Polyneuropathy organomegaly endocrinopathy M-protein and skin changes syndrome with ascites as an early-stage manifestation: A case report
Zhou XL, Chang YH, Li L, Ren J, Wu XL, Zhang X, Wu P, Tang SH
- 143 Devastating complication of negative pressure wound therapy after deep inferior epigastric perforator free flap surgery: A case report
Lim S, Lee DY, Kim B, Yoon JS, Han YS, Eo S
- 150 Adult focal β -cell nesidioblastosis: A case report
Tu K, Zhao LJ, Gu J
- 157 Anesthesia with ciprofol in cardiac surgery with cardiopulmonary bypass: A case report
Yu L, Bischof E, Lu HH
- 164 Thymic lipofibroadenomas: Three case reports
Yang MQ, Wang ZQ, Chen LQ, Gao SM, Fu XN, Zhang HN, Zhang KX, Xu HT
- 172 Perforation of levonorgestrel-releasing intrauterine system found at one month after insertion: A case report
Zhang GR, Yu X
- 177 Drug-induced sarcoidosis-like reaction three months after BNT162b2 mRNA COVID-19 vaccination: A case report and review of literature
Kim SR, Kim SK, Fujii T, Kobayashi H, Okuda T, Hayakumo T, Nakai A, Fujii Y, Suzuki R, Sasase N, Otani A, Koma YI, Sasaki M, Kumabe T, Nakashima O
- 187 Hyponatremic encephalopathy due to polyethylene glycol-based bowel preparation for colonoscopy: A case report
Zhao Y, Dong HS
- 193 Post-traumatic heterotopic ossification in front of the ankle joint for 23 years: A case report and review of literature
Xu Z, Rao ZZ, Tang ZW, Song ZQ, Zeng M, Gong HL, Wen J

- 201** Extraskelatal Ewing sarcoma of the stomach: A rare case report
Shu Q, Luo JN, Liu XL, Jing M, Mou TG, Xie F
- 210** Ochronotic arthropathy of bilateral hip joints: A case report
Yap San Min N, Rafi U, Wang J, He B, Fan L
- 218** Pembrolizumab-induced psoriatic arthritis treated with disease-modifying anti-rheumatic drugs in a patient with gastric cancer: A case report
Kim S, Sun JH, Kim H, Kim HK, Yang Y, Lee JS, Choi IA, Han HS
- 225** High-flow priapism due to bilateral cavernous artery fistulas treated by unilateral embolization: A case report
Li G, Liu Y, Wang HY, Du FZ, Zuo ZW
- 233** Malignant transformation of pulmonary bronchiolar adenoma into mucinous adenocarcinoma: A case report
Liu XL, Miao CF, Li M, Li P
- 242** Cystic artery pseudoaneurysm: A case report
Liu YL, Hsieh CT, Yeh YJ, Liu H
- 249** Congenital stapes suprastructure fixation presenting with fluctuating auditory symptoms: A case report
Choi S, Park SH, Kim JS, Chang J

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Post-traumatic heterotopic ossification in front of the ankle joint for 23 years: A case report and review of literature

Zheng Xu, Zhou-Zhou Rao, Zhong-Wen Tang, Zhen-Qi Song, Ming Zeng, Hao-Li Gong, Jie Wen

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Abstract

BACKGROUND

Heterotopic ossification (HO) refers to the formation of new bone in non-skeletal tissues such as muscles, tendons or other soft tissues. Severe muscle and soft tissue injury often lead to the formation of HO. However, anterior HO of the ankle is rarely reported.

CASE SUMMARY

We report a patient with massive HO in front of the ankle joint for 23 years. In 1998, the patient was injured by a falling object on the right lower extremity, which gradually formed a massive heterotopic bone change in the right calf and dorsum of the foot. The patient did not develop gradual ankle function limitations until nearly 36 mo ago, and underwent resection of HO. Even after 23 years and resection of HO, the ankle joint was still able to move.

CONCLUSION

It is recommended that the orthopedist should be aware of HO and distinguish it from bone tumor.

Key Words: Heterotopic ossification; Post-traumatic; Ankle joint; Case report

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Core Tip: Here we report an adult patient with 23 years of heterotopic ossification at the ankle. After the ankle was injured by a falling object (red brick), a huge bony mass gradually appeared from the ankle to the middle of the calf. The ankle joint remained 30 degree move range after surgery and the range maintained 30 degree in his 1 year follow up, and the radiology showed that there is no recurrence of heterotopic ossification.

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INTRODUCTION

Heterotopic ossification (HO) refers to the formation of new bone in non-skeletal tissues such as muscles, tendons or other soft tissues. HO was first described by Patin in 1692[1]. Subsequently, many scholars have carried out in-depth research on HO. It is generally believed that HO can be divided into two categories[2]: Congenital HO and acquired HO. The former is less common, and mainly caused by gene mutation; there are mainly two diseases: Fibrodysplasia ossificans progressiva (ACVR1 gene mutation) and progressive osseous hyperplasia (GNAS1 gene heterozygous inactivating mutation)[3]. The latter is more common and related to trauma, often due to neurological trauma such as brain and spinal cord injury, severe soft tissue trauma such as burn, explosion injury, musculoskeletal trauma such as fracture, joint dislocation, and surgical trauma such as hip replacement, knee replacement, *etc.*[1, 4, 5].

Here we report an adult patient with 23 years of HO at the ankle. Following injury to the ankle due to a falling object (red brick), a huge bony mass gradually appeared from the ankle to the middle of the calf.

CASE PRESENTATION

Chief complaints

A 67-year-old male patient was admitted in our department due to a mass in front of the ankle joint for 23 years.

History of present illness

In 1998, his right foot was accidentally injured by a brick that fell from a height. He developed pain and swelling in the front of his right foot and calf. He went to a local hospital and was diagnosed with a soft tissue infection. The patient developed a hard mass on the right ankle 3 mo after the injury, about the size of an egg, with no limited ankle joint movement. He then went to the local hospital for treatment and surgery was suggested. The patient did not undergo surgery as the mass did not cause obvious pain and did not affect his joint function.

History of past illness

Three years ago, the patient experienced an accidental sprain of the right ankle with ankle immobility, and was admitted to our department for surgical treatment.

Personal and family history

The patient had no remarkable medical history, no history of hypertension, diabetes, hepatitis, tuberculosis, drugs, or food allergies.

Physical examination

A lump was seen in front of the dorsum of the right foot and the middle and lower part of the calf, which was obvious on the right dorsum; the right calf was slightly swollen, the skin was slightly translucent, there was no obvious tenderness, and the skin temperature was not elevated. The mass on the right dorsum was approximately 6 cm × 7 cm in size (Figure 1) and non-movable, with a hard texture, unclear boundary, unsmooth surface, no obvious tenderness, no obvious boundary with surrounding tissues, and there was no right ankle joint movement. The blood supply, sensation and movement of the extremity were good.



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Figure 1 The appearance of heterotopic ossification in this patient.

Laboratory examinations

Routine blood tests showed that C-reactive protein, erythrocyte sedimentation rate, alkaline phosphatase, blood sugar, and blood trioxypurine were normal.

Imaging examinations

X-ray (Figure 2A) showed a bone mass in front of the right tibia. Computed tomography (CT) (Figure 2B) showed multiple patchy bone masses with uneven bone density in front of the upper segment of the right tibia and the dorsum of the right foot. The edge of the right ankle joint was osteosclerotic with adequate joint space.

FINAL DIAGNOSIS

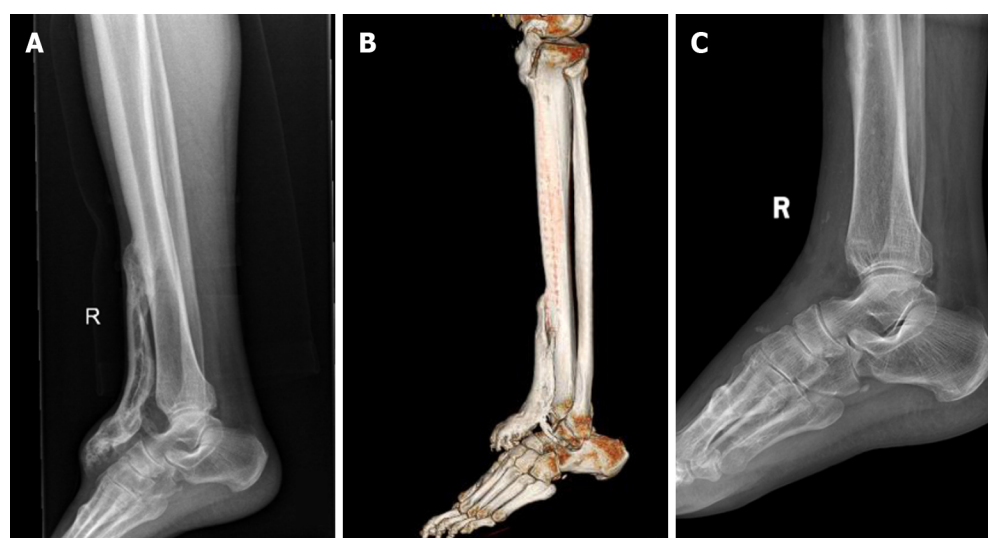
Pathological examination of fibrous connective tissue and bone tissue from the mass on the right dorsum of the foot and the anterior tibia of the calf was performed (Figure 3). Ossification was seen in the muscle tissue in some areas, which was consistent with the changes of myositis ossificans when combined with the clinical and imaging findings. The final diagnosis was HO.

TREATMENT

The patient underwent surgery, and the following procedures were performed: The patient was placed in the supine position on the operating table. After general anesthesia induction and routine disinfection, a sterile drape was placed. When the anterior medial bulge of the right ankle joint was seen, a longitudinal incision of approximately 6 cm was made, the skin and subcutaneous tissue were incised, and the mass was dissociated. The mass was bony, hard and could not be pushed. It started from the middle and lower part of the tibia down to the midfoot. There was a small gap between some parts and the surrounding bone. Ankle joint activity was absent. The bone was first split horizontally. The bone mass surrounded the extensor muscle. The bone mass in front of the ankle joint was excised. The ankle joint was cleaned, the adhering tendons were released, the wound was closed, and the front of the ankle joint was covered with VAC device. The excised mass was sent for medical examination. The operation was successful, and anesthesia was satisfactory. There was little intraoperative bleeding and blood transfusion was not required.

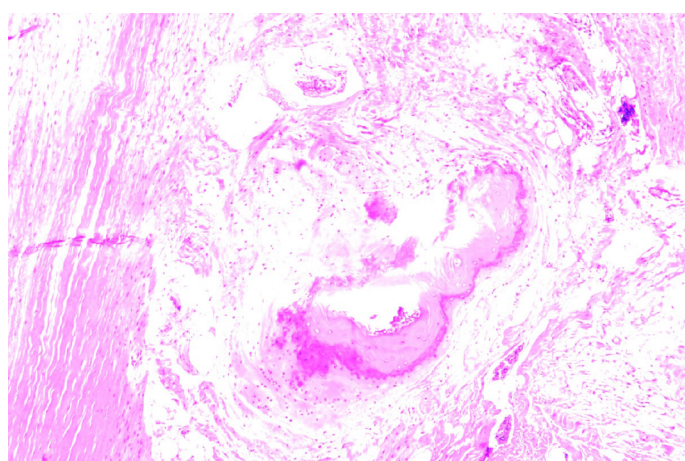
OUTCOME AND FOLLOW-UP

The patient wore an Ankle Foot Orthosis for 4 wk to avoid recurrence of HO, and was allowed to stand and walk 2 wk after surgery. The ankle joint reached a 30 degree range of motion after surgery and this range was maintained during the first year of follow-up. The AOFAS-AH score was 85 after surgery and was maintained at 89 during the first year of follow-up. Radiology showed that there was no recurrence of HO (Figure 2C).



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Figure 2 Radiology findings in this patient. A: X-ray showed that a bone mass was seen in front of the right tibia; B: Computed tomography showed multiple patchy bone masses with uneven bone density in front of the upper segment of the right tibia and the dorsum of the right foot. The edge of the right ankle joint was osteosclerotic with adequate joint space; C: X-ray at follow-up showed that there was no recurrence of heterotopic ossification.



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Figure 3 Biopsy of the bone mass showed ossification in the muscle tissue in some areas, which was consistent with the changes of myositis ossificans when combined with the clinical and imaging findings.

DISCUSSION

Heterotopic ossification refers to the formation of new bone in areas where the bone does not usually appear, such as muscle and soft tissue. It is different from calcification caused by metabolic diseases such as hypercalcemia and malnutrition in tumors, which forms mature lamellar new bone. Histologically, it is indistinguishable from the callus formed by fracture healing. Post-traumatic HO is mainly formed by endochondral osteogenesis. Its formation includes inflammation, chondrogenesis, osteogenesis and ectopic bone maturation[6].

Although the cause of post-traumatic HO is still unclear, it is currently believed that three conditions are necessary for the formation of HO: osteogenic precursor cells, osteogenic-inducing factors, and local promotion of the osteogenic microenvironment. Many multifunctional cells recruit and aggregate at the wound site, such as common mesenchymal stem cells, endothelial cells of mesenchymal stem cells, residual muscle quiescent stem cells (satellite cells) or myogenic progenitor cells, circulating precursor osteoblasts, *etc.*[7-12]. In the process of HO, more and more scholars believe that the local microenvironment is crucial[13,14]. There are two main types of local microenvironment: (1) Inflammatory environment: Many inflammatory cells accumulate in the wound[15], forming an inflammatory response. Current studies have shown that the inflammatory environment is important in forming traumatic HO. Kraft *et al*[16] summarized the role of various immune cells in forming HO, such as

neutrophils, macrophages, mast cells, T and B lymphocytes and natural killer cells. Huang *et al*[6] and others believed that in traumatic tissue, monocyte-macrophages are polarized into M1-M2 macrophages, making mesenchymal cells secrete by the expression of Oncostatin M, transforming growth factor beta1 (TGF- β 1), bone morphogenetic protein (BMP), ActA, surfactant protein, vascular endothelial growth factor (VEGF) and other factors. Stem cells differentiate towards osteogenesis through pathways such as the TGF- β 1-Smad2/3 and BMP-Smad1/5/8 pathways, eventually forming HO. In addition, a large number of inflammatory markers are closely related to the formation of HO, such as interleukin (IL)-3, IL-6, IL-10, IL-12p70, effluent IL-3 and effluent IL-13, MCP-1, effluent IL-10 and MIP-1- α [17-19]; and (2) Hypoxic environment: Tissue hypoxia usually occurs simultaneously after tissue injury. The hypoxic microenvironment is mainly due to the release of inflammatory mediators after severe trauma, leading to the blockage of constrictive blood vessels, resulting in the disorder of tissue blood circulation. Huang *et al*[20] and others believed that the existence of a hypoxic microenvironment leads to the activation of HIF-1 α , which up-regulates the expression of bone morphogenetic proteins and VEGF and down-regulates the expression of neurothelin-1 (NRP-1), resulting in angiogenesis and the proliferation and differentiation of chondrocytes and osteoblasts, eventually forming HO.

Nonetheless, HO is an extremely complex process. Trauma is insufficient to induce HO; other factors such as genetic mutations and neurogenic injury are also required. For example, the induction of neurogenic HO requires traumatic brain injury or spinal cord injury and muscle damage. Pure blast injury cannot cause HO, but severe HO can be induced when combined with a fracture or wound infection, such as a bacterial infection[6]. In addition, severe trauma can often induce HO[21]. It is well known that the accumulation of stem cells and the infiltration of inflammatory cells such as macrophages after tissue injury are beneficial in tissue repair[22]. Recent studies have also suggested that depletion of monocytes/macrophages can lead to the differentiation of recruited endothelial cells towards chondrogenesis[23]. Some scholars believe that severe trauma leads to a severe local and systemic inflammatory response, which makes the repair process out of balance and activates the critical threshold of the BMP signaling pathway to form HO[24]. Therefore, we believe that during the repair of the severe wound on the right calf in this case, due to changes in the local microenvironment, such as severe hypoxia, massive inflammatory cell infiltration, and the consumption of a large number of monocyte-macrophages, the stem cells tend to differentiate into the osteoblast and cartilage, and ultimately form a huge area of HO.

In the early inflammatory stage of the disease course, HO manifests as local pain, swelling, elevated skin temperature, and even fever and erythema, which is similar to cellulitis, thrombophlebitis, and osteomyelitis[1]. As the bone tissue matures in advanced stages, the swelling becomes more localized and firm and may limit movement when close to the joint[15]. The diagnosis of HO in its early stages is difficult due to nonspecific signs and symptoms. This case was misdiagnosed as a soft tissue infection at an early stage, and anti-infective treatment was given, and a huge bony mass gradually formed on the anterior tibia and muscle surface of the right calf and in the subcutaneous tissue of the dorsum of the foot, which eventually led to ankle stiffness. Therefore, we believe that considering the possibility of HO in patients with severe soft tissue trauma, oral non-steroidal anti-inflammatory drugs can be given as an early preventive treatment.

It is currently considered that plain X-ray and three-dimensional CT examination are the gold standards for diagnosing HO, but plain X-ray cannot detect calcification for at least 6 wk after trauma. Although 3D CT is the most sensitive method for detecting HO, it also provides the earliest detection at 2.5 wk after trauma[25]. Bartlett *et al*[26] used a rabbit HO model for early diagnosis and treatment and found that changes in prostaglandins were earlier than bone formation, for example, prostaglandin E2 (PGE2) secretion was significantly increased, reaching a peak at 10 d. Schurch *et al*[27] also found that increasing PGE2 in urine at 24 h suggested HO formation.

The most common sites of post-traumatic HO are the elbow joint in the upper extremity and the hip joint in the lower extremity, especially after total hip arthroplasty[5]. HO occurs relatively rarely at the ankle joint. More recently, as total ankle arthroplasty (TAA) has become a common surgical treatment option for end-stage ankle arthritis, HO at the ankle has been increasingly reported[14]. However, HO is most frequently reported posterior to the ankle joint and rarely anterior to the ankle joint[30]. Although HO is formed after TAA, it does not affect the joint function in patients, and most of them do not require reoperation[14,28]. In this case, a huge HO was formed in the front of the ankle, but it was not until the previous 3 years that the ankle joint movement was gradually limited. The lesion was removed during the operation as HO increased after the ankle sprain and formed a bony connection. Following excision, ankle function recovered. Moreover, during the operation, we found that the HO had wrapped the extensor digitorum tendon and formed a smooth surface with the tendon, which did not affect the free movement of the tendons such as the extensor hallucis longus tendon which formed a tunnel in the HO (Figure 4).

The malignant transformation of HO is rarely reported. In 1981, Eckardt *et al*[29] reported a 32-year-old patient with dermatitis. HO formed on the back of the left thigh when the patient was 8 years old. When the patient was 31 years old, the mass suddenly increased with pain, and the final pathological examination showed that the mass had transformed into a well-differentiated malignant osteosarcoma. Subsequently, in 1999, Aboulafia *et al*[30] reported a 44-year-old female patient who developed diffuse



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Figure 4 The extensor hallucis longus tendon formed a tunnel in the heterotopic ossification.

HO in the soft tissue of the forearm due to electrical burns, which transformed into osteosarcoma 10 years later. Although there are relatively few reports of malignant transformation of myositis ossificans, there are sporadic cases[31]. Although our patient had HO for 23 years, he had no symptoms of malignant transformation, and the postoperative pathological report showed that the mass had no malignant signs.

HO affecting joint function is an absolute indication for surgical resection. However, there was recurrence after surgery. Agarwal *et al*[32] and other studies have found that postoperative recurrence has nothing to do with unresected HO, not the enlargement of residual lesions, and the same mechanism as the original HO. In the current study, following HO resection, the ankle joint was still able to move, which indicated that the earlier the HO resection is performed, the better the joint function will be.

CONCLUSION

It is recommended that the orthopedist should be aware of HO and distinguish it from bone tumor.

FOOTNOTES

Author contributions: Xu Z and Rao ZZ contribute equally to this study, they share co-first author, Tang ZW conceived and coordinated the study, designed, Song ZQ and Zeng M performed and analyzed the experiments, Xu Z wrote the paper; Gong HL and Wen J did the follow-up with the patients; JW did the data analysis and carried out the data collection and revised the paper.

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