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Heterotopic Mesenteric Ossification after Hemicolectomy for Colon Cancer

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Background	Heterotopic mesenteric ossification (HMO) is an extremely rare condition of abnormal bone formation in the intestinal mesentery that may have severe complications. Very few HMO cases have been reported in the literature with an association with trauma, abdominal surgery, and burns; however, the exact mechanism is still poorly understood.
Summary	In this report, we present a case of a 73-year-old patient with colon adenocarcinoma who underwent an extended right hemicolectomy and ileotransverse anastomosis. His postoperative course was complicated by anastomosis leakage, peritonitis, and pancreatic fistula. After seven months, he had an ileostomy reversal procedure when he was found to have multiple bone fragments within the mesentery. Pathology examination was consistent with the diagnosis of HMO.
Conclusion	We report an extremely rare case of an extended right hemicolectomy for colon adenocarcinoma complicated by anastomosis leakage and pancreatic fistula before developing HMO after seven months.
Key Words	heterotopic ossification; heterotopic mesenteric ossification

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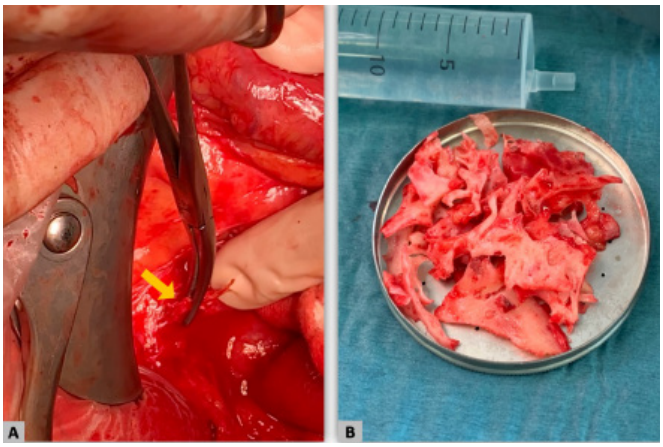
Case Description

A 73-year-old male with a past medical history of hypertension, psoriasis, and remote appendectomy in his childhood was admitted to the hospital for abdominal bloating and fullness. An abdominal CT scan showed a right colon mass in the hepatic flexure. A follow-up colonoscopy and biopsy confirmed the malignancy. He had an extended right hemicolectomy (ERH) with a side-to-side Ileotransverse anastomosis. The final pathology report demonstrated pT3 N0 moderately differentiated invasive adenocarcinoma. His postoperative course was complicated by anastomosis leakage, pancreatic fistula, and peritonitis. The laboratory results of the drained abdominal fluid were significant for high amylase of 1013 IU/l and high lipase of 6000 IU/l, confirming pancreatic fistula. He was sent back to the operating room for relaparotomy. Intraoperatively, the decision was made to resect the ileotransverse anastomosis along with the left colic flexure before creating an end ileostomy.

Five weeks later, the patient's postoperative course was also complicated by pulmonary embolism, and he received anticoagulation. Due to anticoagulation therapy and upon the patient's request, the decision to perform the ileostomy reversal procedure was delayed until seven months after the right colectomy surgery. During the stoma reversal surgery, the ileostomy was relocated back with an ileo-descending colon anastomosis. Extensive adhesions were identified along with multiple bone-like fragments in the mesentery. These fragments varied in size with occasional angulated edges. (Figure 1A) They were limited within the mesentery, and no intraabdominal organ injury was identified. The removal of the fragments was surgically challenging to keep the internal organs and nearby vessels intact. Most of the fragments were removed (Figure 1B) and sent to the pathology department for further assessment.

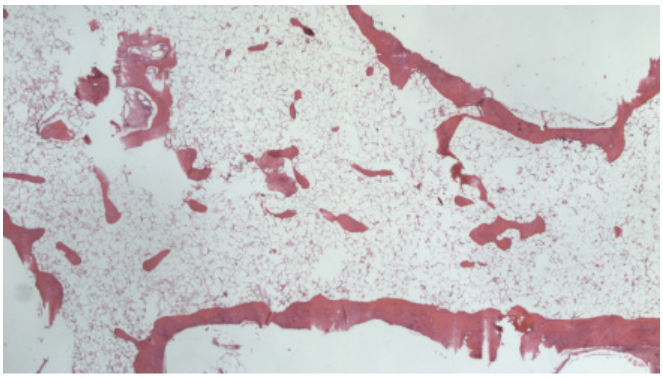
Pathology examination showed approximately 30 white-tan firm irregular bone fragments ranging from 2.0 × 2.0 × 0.1 cm up to 12.0 × 7.0 × 0.2 cm. Histology examination demonstrated mature lamellar bone without rimming osteoblastic activity. Marrow fat intermingled with the occasional hematopoietic element; few bland spindle cells were present. However, no significant cytological atypia, atypical mitosis, or necrosis were identified (Figure 2). This morphology, along with the history of recent abdominal surgery, rendered a diagnosis of heterotopic mesenteric ossification (HMO).

Figure 1. Intraoperative Images. Published with Permission



A) Intraoperative identification of bone fragment with an angulated edge within the intestinal mesentery (yellow arrow). B) Surgical removal of multiple bone fragments in varying sizes.

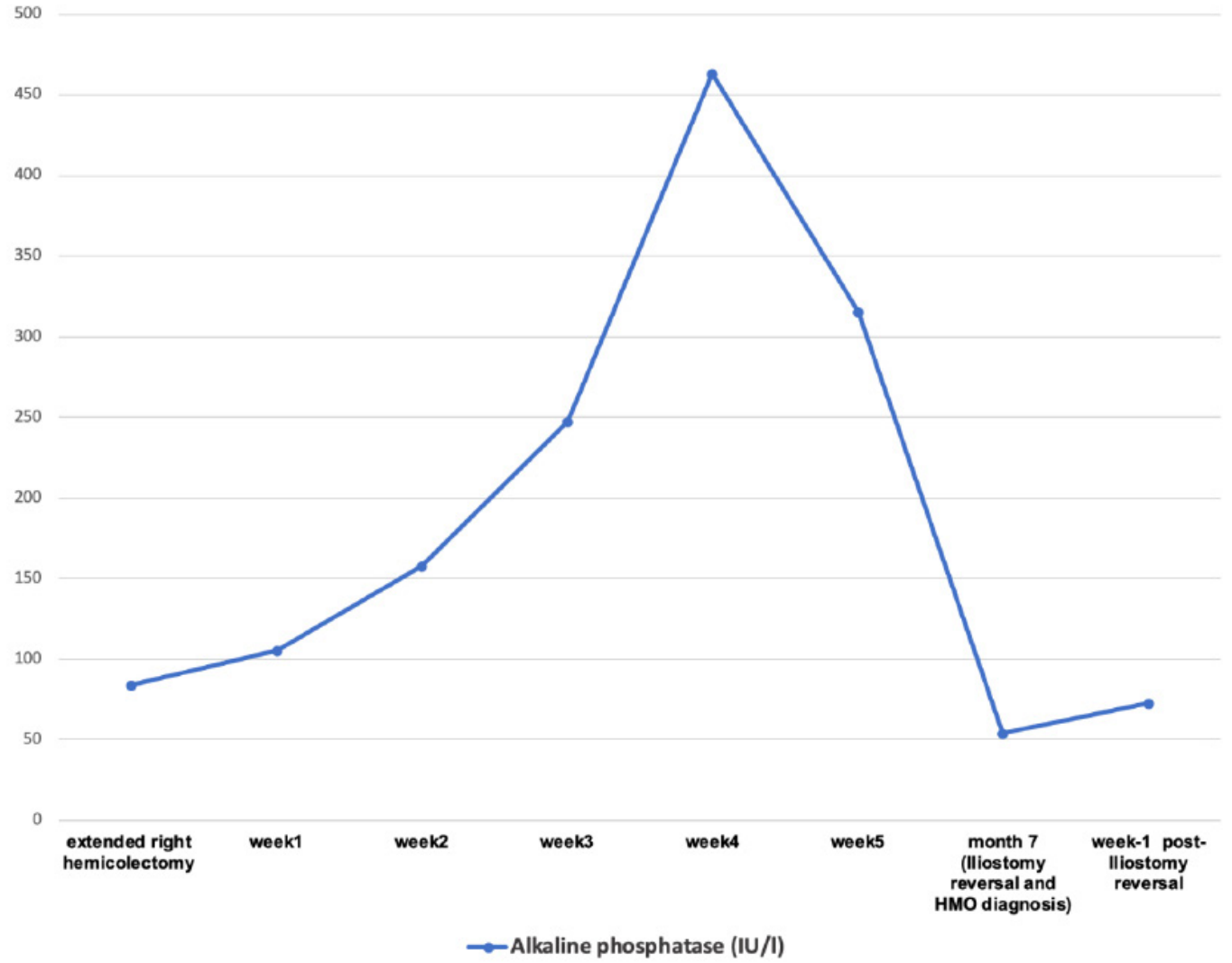
Figure 2. Histologic Examination of Mature Lamellar Bone. Published with Permission



Section shows mature lamellar bone with marrow fat, an occasional hematopoietic element, and few bland spindle cells. No significant cytological atypia, atypical mitosis, or necrosis was identified.

The laboratory results showed a gradual increase in alkaline phosphatase (ALP) levels following the right hemicolectomy, with a peak of 455 IU/I in the fourth week (Figure 3). Afterward, ALP gradually declined until the ileostomy reversal procedure and the identification of the bone fragments and HMO diagnosis. The patient did well and was symptom-free in a six-month follow-up visit.

Figure 3. Graph Depicting Gradual Increase of ALP Level Following Right Hemicolectomy.



Note peak around the fourth week before progressive decrease until bone fragments identification and HMO diagnosis after seven months during an ileostomy reversal procedure.

Discussion

Heterotopic ossification (HO) is an uncommon entity of abnormal bone formation in soft tissue. Riedel first described this bone growth in 1883 as a complication of spinal cord injury.[1] Heterotopic ossification of the intestinal mesentery has previously been described under different names such as "mesenteritis ossificans,"[2] "intraabdominal myositis ossificans,"[3] and recently "heterotopic mesenteric ossification (HMO)". It is an extremely rare condition that results in intraabdominal ossification of unknown origin and can lead to severe complications. Hansen et al.[4] and Lemeshev et al.[5] first described HMO in 1983. Afterward, Wilson et al. reported five cases of intraabdominal HMO in 1999.[3] The exact etiology is poorly understood.[6,7] However, some authors suggested that HMO is a reactive process rather than a neoplastic entity. They proposed that osteoprogenitor cells differentiate into osteoblasts or chondroblasts, resulting in abnormal bone formation in HMO.[8-10]

HMO can be acquired or rarely hereditary form. The acquired form is the most common and is primarily associated with trauma, burns, abdominal surgery and/or

intestinal obstruction, enterocutaneous fistula, and peritonitis.[11,12] Other rare associations such as benign polyps, colon and stomach carcinoid tumors, and appendix mucoceles have been reported.[13] Conversely, the rare hereditary form includes myositis ossificans progressiva, also known as fibrodysplasia ossificans progressiva (FOP) or Münchmeyer disease. It is an extremely rare autosomal dominant connective tissue disorder characterized by progressive fibrosis and ossification of muscles, tendons, and fasciae of multiple sites, along with skeletal abnormalities, including great toe malformation, deafness, and baldness.[14,15] In our case, the patient had a hemicolectomy with a complicated pancreatic fistula, as confirmed by abdominal fluid analysis. While it is unclear whether his HMO development is related to hemicolectomy or pancreatic fistula, pancreatitis and pancreatic fistula are usually associated with calcification rather than ossification. Yet, distinguishing between these two related events and assigning a culprit in such a case is almost impossible.

Honjo and his colleagues reported 33 intraabdominal heterotopic ossifications in the literature with male predilection and an average age of 53 years. The most common complications are intestinal obstructions, followed by abdominal mass formation and fistula formation. Ossification occurs mainly in the mesentery and less commonly in the omentum.[16] Although infrequent in this age group, HMO was reported in a 14-year-old boy with anorectal malformation and rectourethral fistula following colostomy and posterior sagittal anorectoplasty.[17]

Diagnosing HMO preoperatively is challenging yet important, not only due to its potentially severe complications, such as intestinal obstruction and bowel perforation but also because of its potential to be mistaken for malignancy.[11,18] CT scan is currently the best imaging modality for HMO diagnosis. It can demonstrate HMO progressive changes, including identifiable cortical and trabecular architecture.[19] Our patient had a chest CT scan when pulmonary embolism was suspected; however, no abdominal CT scan prior to the re-exploration was indicated or performed. On the other hand, X ray may also be useful in the diagnosis, though it will not detect the lesion until five weeks.[11,19] Radionuclide bone scan is a sensitive method as it shows increased uptake in the course of HMO before becoming evident on plain films; however, it is not specific for HMO.[15] Other modalities such as technetium-99m-methyl diphosphonate single-photon emission computed tomography/computed tomography (Tc-99m MDP bone SPECT/CT) and three-dimensional CT (3D CT) scans may also have diagnostic use.[9,20]

The laboratory findings may play a role in the diagnosis of HMO. Few reports in the literature suggested that alkaline phosphates (ALP) may serve as a sensitive marker for HMO as an increased level reflects osteoblastic activity and heterotopic bone formation. HMO usually grows and develops within two to three weeks following abdominal trauma or surgery.[4] Interestingly, ALP often gradually increases and reaches the peak level within three to four weeks.[11,18,21] Our presented patient showed similar findings with ALP peak at the fourth week. Other studies showed that ALP levels reach approximately 3.5 times the normal value ten weeks after the inciting trauma and return to normal levels at approximately 18 weeks. However, ALP levels can be normal despite HMO activity or may remain elevated for years.[22] Measurement of the 24-hour prostaglandin-E2 (PGE2) urinary excretion has also been a sensitive indicator of early HMO. Anti-PGE2 agents, including indomethacin, is effective in slowing the disease process.[23]

Pathology examination remains the cornerstone for HMO diagnosis. The histology examination shows nodules of dense fibrous tissue with bone trabeculae showing a "zonation pattern." There is classically progressive maturation from the central (inner zone) consisting of loosely arranged reactive spindle cells with prominent mitotic figures, to the middle zone of organized osteoid, to the most mature lamellar bone at the peripheral zone of the lesion. This phenomenon, known as the "zonation pattern," is usually seen in early lesions, and it is a classic histology feature of HMO. However, those reactive cells lack atypical mitosis, significant cytological atypia, and necrosis. As the lesion matures, lamellar bone with marrow fat or hematopoietic trilineage may dominate. However, the mature bone-rimming osteoblastic cells do not show significant cytological atypia or necrosis.[11,12,24] Our patient was diagnosed at a late stage, after at least a few months of the lesion development, and our pathology findings are consistent with the latter.

Lesions showing high cellularity and frequent atypical mitotic figures raise concern for extraskeletal osteosarcoma (ESOS), a challenging histologic differential diagnosis.[25] Unlike the classic zonation pattern of early HMO, ESOS frequently shows a "reverse zonation" pattern, with increasingly immature cells at the periphery rather than the center of the lesion.[26] ESOS also shows malignant features, at least focally, including coagulative necrosis, hyperchromasia, nuclear irregularity, bizarre nuclear forms, and atypical mitotic figures. A clinical history of recent abdominal surgery or trauma would favor an HMO diagnosis.[27]

HMO is usually a self-limiting disease and may go into regression; however, recurrence is also reported. Owing to the rarity of these lesions, the conclusive therapeutic strategy for HMO is still controversial. However, surgical therapy should be conservative, with only simple resection of involved bowel segments and lysis of adhesions. Maintaining intact internal abdominal organs and surrounding blood vessels during HMO and bone fragment removal surgery is a delicate procedure requiring highly skilled surgeons. Non-steroidal anti-inflammatory drugs (NSAIDs), diphosphonates, cimetidine, and radiotherapy may be useful in treatment and the prevention of recurrence.[28] NSAIDs have successfully been used as prophylaxis for HMO in patients undergoing total hip arthroplasty.[29] Diphosphonates have been recommended as soon as detection of ALP elevation or imaging findings of HMO.[30] However, their application is still controversial.

Conclusion

We reported an extremely rare case of an extended right hemicolectomy for colon adenocarcinoma that was complicated by anastomosis leakage and pancreatic fistula before developing HMO after seven months.

Lessons Learned

A detailed clinical history and careful microscopic examination are important for distinguishing HMO from extraskeletal osteosarcoma. Owing to the rarity of these lesions, the conclusive therapeutic strategy for HMO is still controversial. However, surgical intervention is the treatment of choice in symptomatic patients. Prophylactic therapy for potential recurrence is quite debatable.

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