Malaysian J Pathol 2016; 38(1) : 49 – 54

CASE REPORT

Heterotopic ossification in appendiceal mucinous neoplasms: clinicopathological characteristics of 3 cases

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Abstract

Heterotopic bone formation is a very rare event in the gastrointestinal tract including in the appendix. Here we report three cases of heterotopic ossification in appendiceal mucinous neoplasms, one occurring in an appendiceal mucinous cystadenoma, another in a low-grade appendiceal mucinous neoplasm, and the third occurring in an appendiceal mucinous adenocarcinoma. The clinicopathologic characteristics of these three present cases and two previously reported cases are discussed in detail. The mechanism of heterotopic ossification in appendiceal mucinous neoplasm is still unclear, but mucin extravasation and subsequent calcification may be predisposing events.

Keywords: heterotopic ossification, appendix, appendiceal mucinous neoplasm.

INTRODUCTION

Heterotopic ossification (HO) has been reported in a variety of malignancies including those involving the kidney, liver, breast, and lung.[1] HO in the gastrointestinal tract is exceedingly rare and has been reported in association with rectal adenocarcinoma, gastric carcinoid, and adenomatous or non-adenomatous polyps.[2-5] Dystrophic calcifications in appendiceal mucinous neoplasms are not uncommon events, but heterotopic ossification is extremely rare. Only two case reports have been described in the English literature.[6, 7] Here, we describe the clinicopathological characteristics of 3 cases of mucinous appendiceal neoplasms with dystrophic calcification and HO, to increase awareness of this uncommon phenomenon.

CASE REPORT

Case 1

A 44-year-old woman with a history of total thyroidectomy for papillary carcinoma 5 years previously was undergoing follow-up. During PET CT, a region of hypermetabolism, measuring 3.4 cm in diameter, was found in the caecal area (Fig. 1). On admission, her vital signs were within normal limits and a physical examination conducted at presentation revealed no remarkable findings. Laboratory tests results were within normal limits. The patient subsequently underwent resection of the caecum and appendix. The patient has been followed up for 30 months with no evidence of disease.

Pathology

The resected specimen consisted of the caecum and appendix with periappendiceal soft tissue measuring 4.5cm in length. The base of the appendix was grossly dilated and the remainder of the appendix up to the tip showed a narrow and fibrotic appearance. The mucosa of the caecum was unremarkable. On cut section, the proximal portion of the appendix was slightly dilated and was filled with mucoid material and several yellow-tan, gritty areas were identified in the submucosa of the caecum and appendix (Fig. 2A). Microscopically, a mucinous cystadenoma was identified at the base of the appendix, extending upward to the caecal mucosa (Fig. 2B). There were several foci of calcification with heterotopic ossification in the submucosa (Fig. 2C) and the osseous metaplasia was composed of immature trabecular bony spicules surrounded by a rim of osteoblasts (Fig. 2D).

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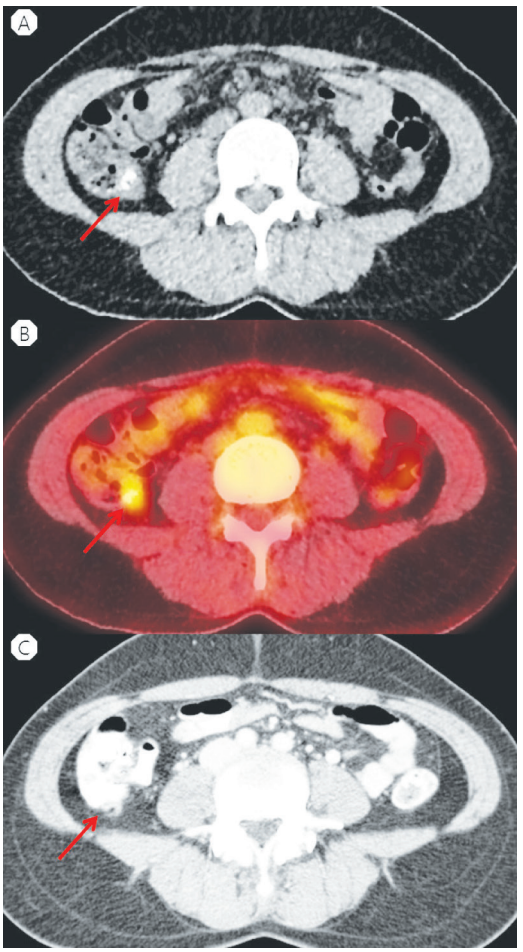

FIG. 1: CT and PET scan of case 1. (A) On the non-enhanced CT scan, focal hyperdensity (arrow) is noted at the ostium of the appendix, probably representing calcification or ossification. (B) On the PET-CT scan, abnormally increased metabolism is noted in the hyperdensity region (arrow). (C) On the contrast enhanced CT scan, no definite enhancing lesion is noted at this area (arrow).

Case 2

A 56-year-old female presented with abdominal pain for 3 months. On ultrasonography, a 7-cm-sized appendiceal mass was detected. On CT scan, an oval, low-density mass was present in the right lower quadrant. The mass originated from the caecal base with no infiltration into the surrounding fat. A 0.4 cm-sized renal stone was identified in the left kidney. Ileocecectomy was performed. The patient has been followed up for 9 years without tumour recurrence.

Pathology

The resected specimen consisted of an ileum and caecum with the appendix showing a dilated cystic mass (Fig. 3A). The base of the appendix was widened and filled with mucoid material. Histologically, a low-grade appendiceal mucinous neoplasm was evident and showed circumferential replacement of neoplastic mucosa with a loss of underlying lymphoid tissue and fibrosis of the submucosa (Fig. 3B). The neoplastic mucosa appeared almost flat with occasionally undulating architecture (Fig. 3B, inset). Dystrophic calcification was identified (Fig. 3C) and heterotopic ossification was noted in its centre (Fig. 3D).

Case 3

A previously healthy, 58-year-old female presented with an incidentally detected pelvic mass. On CT scan performed at an outside hospital, a preliminary diagnosis of right ovarian carcinoma with peritoneal carcinomatosis was made. Open surgical exploration was performed. After a midline incision was made, the pelvic cavity was found to be filled with mucinous material and the tumour seemed to originate from the appendix. Under a working diagnosis of pseudomyxoma peritonei, a right hemicolectomy was performed by the general surgeons. The patient has been on follow up for 5 years without recurrence or metastasis.

Pathology

The resected specimen consisted of the ileum, caecum, ascending colon, and appendix. The appendix was covered with ruptured mucinous tumour measuring 8.0x7.5cm (Fig. 4A). Cut section showed a dilated appendix filled with tenacious mucoid material and destructive invasion of the appendiceal wall was noted (Fig. 4B). Microscopically, mucinous cystadenocarcinoma was present. Complex epithelial proliferation of atypical glands with nuclear stratification and atypia were present (Fig. 4C), and focal stromal invasion was identified (Fig. 4C, inset). In another area, heterotopic ossification was noted adjacent to the neoplastic appendiceal mucinous epithelium (Fig. 4D).

DISCUSSION

Heterotopic ossification (HO) refers to bone formation at an abnormal location outside the normal skeleton. The criteria of HO are the presence of bone cells and collagenous matrix as well as absence of cellular atypism.[8] Typical

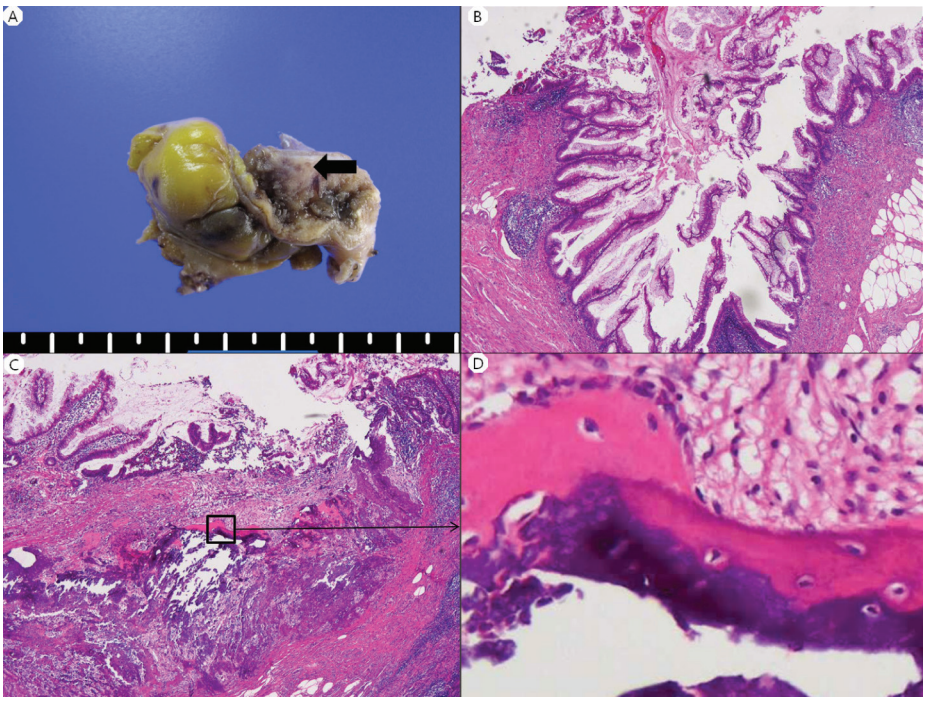

FIG. 2: Gross and microscopical features of case 1. (A) Cut section reveals several gritty areas in the submucosal area (arrow). (B) Noninvasive adenoma is confined to the appendiceal mucosa (HE, x40). (C) Submucosal dystrophic calcification with heterotopic ossification is present (HE, x200). (D) On high power view, immature trabecular bony spicules are present that are surrounded by a rim of osteoblasts.

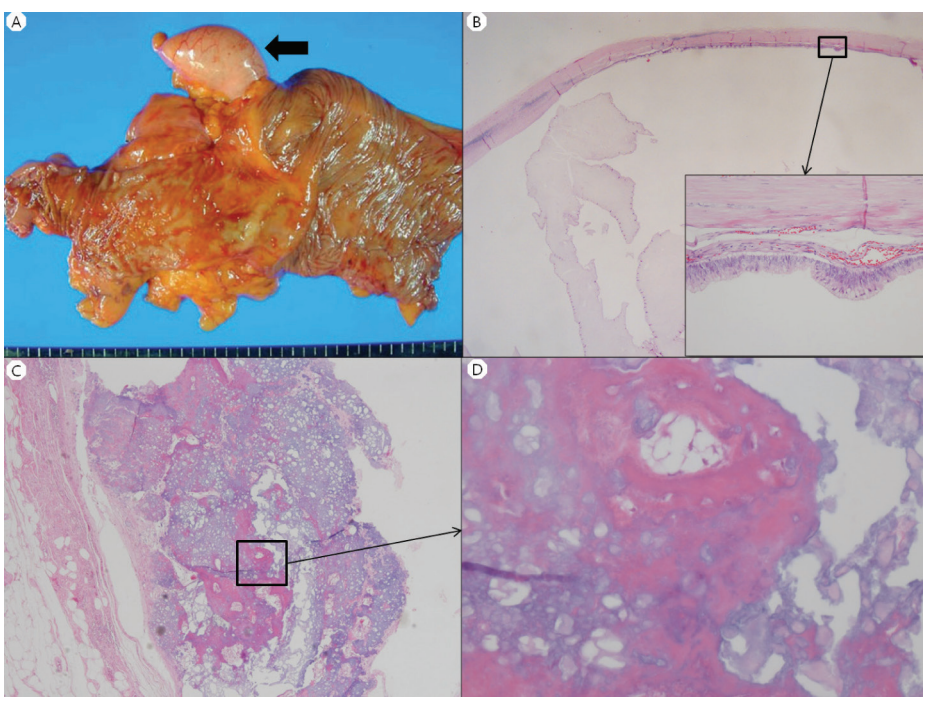

FIG. 3: Gross and microscopical features of case 2. (A) An enlarged, dilated cystic appendiceal mass is noted (arrow). (B) On scanning view, a low-grade appendiceal mucinous neoplasm shows a unilocular cystic mass with a flat and undulating neoplastic mucosa (inset). (C) A dystrophic calcification is noted (HE x40). (D) In the centre, heterotopic ossification is noted (HE, x400).

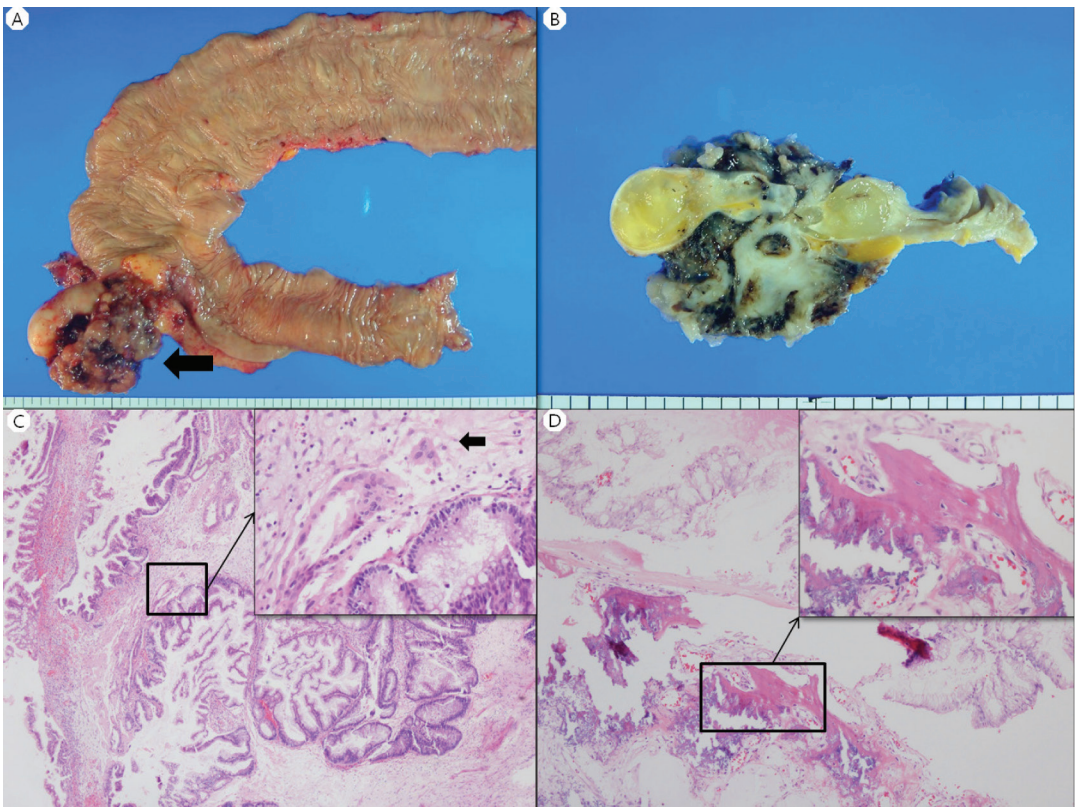

FIG. 4: Gross and microscopical features of case 3. (A) Gross photography shows a dilated appendix with a ruptured mucinous tumor. (B) Cut section reveals destructive invasion of the appendiceal wall with a dilated appendiceal lumen filled with thick mucinous material. (C) Complex glandular epithelial proliferation with atypical nuclear stratification is noted (HE, x40). Stromal invasion is focally present (inset, arrow). (D) Heterotopic ossification is present adjacent to the neoplastic appendiceal mucosa (HE, x40). Immature trabecular bony spicules are noted (inset).

acquired HO is a common complication of various types of traumatic events.[9, 10] However, HO in the gastrointestinal tract is rare. Fewer than 100 cases of have been described in the literature.[6] In contrast, dystrophic calcification is defined as the deposition of calcium salts in abnormal tissue such as scar tissue or atherosclerotic plaques.

In this report, we described 3 cases of mucinous appendiceal neoplasms with HO. The clinicopathological data of the cases here as well as previously reported cases are summarized in Table 1. All but one patient was female (4/5, 80%). The patients' ages ranged from 44 to 70 years and the tumour size ranged from 2 cm to 8 cm. One patient presented with an inguinoscrotal hernia, but the tumour was incidentally found in the other patients. Two patients had a history of ulcerative colitis and papillary thyroid carcinoma, respectively. Clinically, all but one case originated from the base of appendix. The pathological diagnoses included 1 case of mucinous cystadenoma, 2 cases of low-grade appendiceal mucinous neoplasm and 2 cases of mucinous cystadenocarcinoma. In one case by Juvara *et al.*,[7] a diagnosis of mucocele was made but the possibility of low-grade appendiceal mucinous neoplasm was raised because the findings of pseudomyxoma peritonei with appendiceal rupture were mentioned in the gross description. In all cases, the HO was associated with pre-existing extracellular mucin and dystrophic calcification. With advancements in CT and PET, calcification can be detected prior to operations.

The incidence of mucinous appendiceal neoplasms is relatively low. Appendiceal mucinous neoplasms are uncommon, making up 0.2% to 0.3% of all appendectomy specimens.[11] Dystrophic calcifications can be associated with mucinous appendiceal neoplasms, but the incidence is still unknown. In two studies, appendiceal wall calcifications were found in

TABLE 1: Clinicopathological data of the five present and reported cases of appendiceal mucinous neoplasm with heterotopic bone formation

Cases	Sex/ Age	Past history	Site	Ca++	Diagnosis	Size (cm)	Follow-up
Juvara *et al.*[7] (1948)	M/70	Inguinoscrotal hernia with strangulation	Base	Present	Mucocele (R/O low-grade appendiceal mucinous neoplasm)	7	6 mo, NED
Haque *et al.*[6] (1996)	F/46	UC (long history)	Base	Present	Mucinous cystadeno-carcinoma	2	NA
Case 1	F/44	PTC (5 yr)	Base	Present	Mucinous cystadenoma	3.5	30 mo, NED
Case 2	F/56	None	Base	Present	Low-grade appendiceal mucinous neoplasm	7	9 yr, NED
Case 3	F/58	None	Body	Present	Mucinous cystadeno-carcinoma	8	5 yr, NED

Abbreviations: M, male; F, female; yr, year; mo, months; UC, ulcerative colitis; PTC, papillary thyroid carcinoma; Ca++, calcification; R/O, rule out; NA, not available; NED, no evidence of disease.

4 (23.5%) of 11 cases and 5 (29.4%) of 17 cases.[12, 13] However, HO is rarely reported and only 2 cases have been reported in the English literature to date.

Many literature reviews have demonstrated that HO is observed in different histological settings. However, the cause of HO is controversial. Various histological features of tumours have been associated with HO including necrosis, inflammation, increased stromal vascularity, extracellular mucin deposition and pre-existing calcification.[14] The secretion of mucin by tumour cells, usually in minimal quantities, has been observed in many of the reported cases.[15] The mechanism underlying HO is still a matter of controversy, but mucin extravasation and subsequent dystrophic calcification is suggested to be one such mechanism. This may be one of the reasons why the occurrence of dystrophic calcification is more commonly identified than HO in appendiceal mucinous neoplasms.

HO in gastrointestinal cancers appears to result from tumour production of bone morphogenic protein (BMP).[6] BMPs are characterized as low-molecular-weight glycoproteins that act as cytokines that generally target immature, multipotent cells and cause the stimulation of mesenchymal differentiation into osteoblasts.[16] Thirteen subgroups of BMPs have been discovered, and all but BMP-1 is thought to have osteogenic effects.[16] Among the BMP subgroups, BMP-2, -4, and -7 have been reported to have the ability to induce ectopic bone formation.[17] In addition to BMPs, TGF-ß appears to play a role in the formation of HO. In mammals, TGF-ß1, ß2, and ß3 have been identified. Different TGF-ß isoforms and their receptors exhibit distinct but overlapping patterns of expression during bone formation.[18] BMP-2, TGF-ß2, and TGF-ß3 are suggested to be involved in heterotopic bone formation.[19]

Conclusion

We present 3 extremely rare cases of HO in the setting of appendiceal mucinous neoplasms with a literature review of the 2 previously reported cases. Preoperative CT scan showed areas of calcification within the tumours in the three present cases and preoperative PET scan detected an area of increased hypermetabolism in one case. Importantly, the tumours had no area of necrosis, contained mucin pools, and had ectopic benign

bone formation. The exact mechanism of HO is unclear, but mucin extravasation and subsequent dystrophic calcification may contribute to ectopic bone formation. Awareness of the potential for HO with dystrophic calcification in appendiceal mucinous neoplasms is important because of its clinical relevance.

ACKNOWLEDGEMENT

The authors declare no conflict of interest.

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