CASE REPORT

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Diffuse and psammomatous calcification in intestinal type gastric carcinoma: Report of two cases with literature review

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Psammoma bodies are round, concentrically laminated calcospherites ranging from 5 to 100 µm in diameter. They may indicate certain types of tumors including papillary carcinoma of the thyroid, meningioma and papillary serous tumors of the ovary, and to a lesser extent may be found in leiomyomas and angiomas of the gastrointestinal tract. Dystrophic calcification is uncommon in gastric cancer and displays either diffuse or psammomatous pattern. Diffuse type calcification is generally seen within the pools of mucin in advanced mucinous adenocarcinoma. Conversely, psammomatous calcification is associated with non-mucin- producing carcinomas and detected not only within the carcinomatous glandular lumina but also in the stroma. Total gastrectomy specimens of a 74-year-old male and a 54-year-old female with moderately differentiated intestinal type adenocarcinomas revealed diffuse and psammomatous calcification, respectively. Although diffuse type calcification is well-documented, to date it has not been reported in non-mucin-producing intestinal gastric carcinoma. Moreover, the psammomatous type is exceptionally rare, and only six such cases have been reported in the literature; the current patient represents the seventh case.

Key words: Gastric carcinoma, diffuse calcification, psammomatous calcification

İntestinal tıp gastrik adenokarsinomda diffüz ve psammomatöz kalsifikasyon: İki olgu eşliğinde literatürün gözden geçirilmesi

Psammoma cisimleri çapı 5-100 mikrometre arasında değişen yuvarlak, konsantrik tabakalı kalkosferitlerdir. Tiroidin papiller karsinomu, menengiom ve overin papiller seröz tümörleri dahil olmak üzere belirli tümör tiplerini işaret edebilirler; daha az bir oranda gastrointestinal sistemdeki leiomyomlar ve anjiomlarda bulunabilirler. Mide kanserlerinde diffüz kalsifikasyon nadirdir ve ya diffüz ya da psammomatöz formda görülürler. Diffüz tip kalsifikasyon, genellikle ilerlemiş müsinöz adenokarsinomlarda müsin gölcükleri içinde görülür. Bunun tersine, psammomatöz kalsifikasyonlar müsin üretmeyen karsinomlarla ilişkilidir ve sadece karsinomatöz glandların lümeninde değil, ayrıca stromada da saptanır. Orta derecede diferansiye intestinal tip adenokarsinomu bulunan 74 yaşındaki erkek ve 54 yaşındaki kadın hastanın total gastrektomi materyallerinde, sırasıyla diffüz ve psammomatöz kalsifikasyon saptandı. Diffüz tip kalsifikasyon iyi bilinmesine rağmen bugüne kadar müsin üretmeyen intestinal tip gastrik karsinomlarda bildirilmemiştir. Ek olarak, psammomatöz tip oldukça nadir görülür ve literatürde bugüne kadar 6 olgu bildirilmiştir; sunduğumuz olgu yedinci olgudur.

Anahtar kelimeler: Gastrik karsinom, diffüz kalsifikasyon, psammomatöz kalsifikasyon

INTRODUCTION

Psammoma bodies are well-circumscribed round, concentrically laminated calcospherites ranging from 5 to 100 µm in diameter, and can be seen in a range of conditions (1,2). They may indicate certain types of tumors including papillary carcinoma of the thyroid (2,3), meningioma (4,5), duodenal

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carcinoid (also called adupoma) (6), odontogenic cysts (7), soft tissue neoplasms (e.g. fibrous pseudotumor) (8), and especially common in the female, genital tract neoplasms (e.g. papillary serous tumor of the ovary, adenocarcinoma of the endometrium) (9,10). In addition, they can be seen in tumors originating from other organs such as the breast, lung, kidney, pituitary gland, colon (11), and stomach (12-17). Dystrophic calcification is uncommon in gastric cancer and displays either mucin pool diffuse calcifications or psammomatous pattern (17). Diffuse type calcification is generally seen within the pools of mucin in advanced diffuse type mucinous adenocarcinoma. Conversely, psammomatous calcification is associated with non-mucin-producing intestinal type carcinomas and detected not only within the carcinomatous glandular lumina but also in the stroma (17,18). Heterotropic ossification, another type of calcification, is associated with well-differentiated adenocarcinoma and may be seen in primary and metastatic localization (18). Here, we present two cases of gastric calcification - one diffuse and one psammomatous - which developed in intestinal type gastric adenocarcinomas, and we discuss the cases together with the literature.

CASE REPORTS

Case 1

Endoscopic examination of a 74-year-old man who presented with loss of appetite, nausea, epigastric pain, and vomiting exhibited a tumoral mass commencing just below the Z line, mainly located in the lesser curvature. Multiple endoscopic biopsies were taken. Abdominal X-ray examination and computerized tomography (CT) of the whole abdomen was unremarkable. Routine laboratory tests including serum calcium and phosphate were in normal limits. Subsequent to pathologic diagnosis of adenocarcinoma, subtotal gastrectomy was performed. Gross examination revealed a 7x5x2.5 cm tumor, white to gray in appearance and infiltrating the esophagus. Microscopic examination showed atypical columnar cells with eosinophilic cytoplasm, hyperchromatic nuclei and prominent nucleoli forming glandular structures containing widespread diffuse dystrophic calcification, particularly in necrotic areas (Figure 1A). The tumor invaded the entire gastric wall including the serosa. Of nine metastatic lymph nodes, no calcification was seen. Liver metastasis developed after seven months and the patient was lost to follow-up.

Case 2

A 54-year-old woman presented with loss of appetite, weight loss and epigastric pain. Endoscopic examination revealed a tumor with ulceration and necrosis extending along the lesser curvature, and multiple biopsies were taken. Abdominal X-ray examination and CT of the whole abdomen were unremarkable. Routine laboratory tests including serum calcium and phosphate were in normal limits. Subsequent to pathologic diagnosis of adenocarcinoma, the patient underwent total gastrectomy and omentectomy. On gross examination, a 6x4.5x2 cm tumor with firm consistency involving the entire lesser curvature, invading the anterior and posterior gastric wall, esophagus and serosa was observed. Microscopically, moderately differentiated intestinal type gastric adenocarcinoma was detected demonstrating glandular structures, some of which were aberrant, containing atypical columnar cells with eosinophilic cytoplasm, hyperchromatic nuclei and prominent nucleoli, and infiltrating the whole cut surface including the serosa. Basophilic, round-to-oval psammoma bodies with central lamination and irregular margins were noted confined in the tumor, particularly congregating in the more central areas of the glands (Figure 1B) stained with von Kossa (Figure 1C). No mucin production was perceived. Of nine metastatic lymph nodes, neither psammoma bodies nor other type of calcification was seen. Liver metastasis developed after eight months and the patient was lost to follow-up at 10 months.

DISCUSSION

Although several theories have been proposed, the process of the pathologic calcification in gastric adenocarcinoma has not been identified exactly (19-21). It has been presumed that the decrease in cellular respiration and carbon dioxide production due to insufficient blood supply secondary to ischemia and necrosis in the stomach results in relative alkalinity, and since calcium salts are hardly soluble in alkaline solutions, subsequent precipitation of calcium salts (18-20,22). It has also been suggested that mucin, a glycoprotein, has a predilection for calcification that may act as a nidus (19,20). Because of the similarity of glycoprotein consistency in mucin-containing gastric adenocarcinoma and epiphyseal cartilage of the growing bone, which is believed to play an important role in calcification (23), ontogenetic calcification has also been considered in calcified mucinous gastric carcinomas. Prolonged vomiting as noted in the cur-

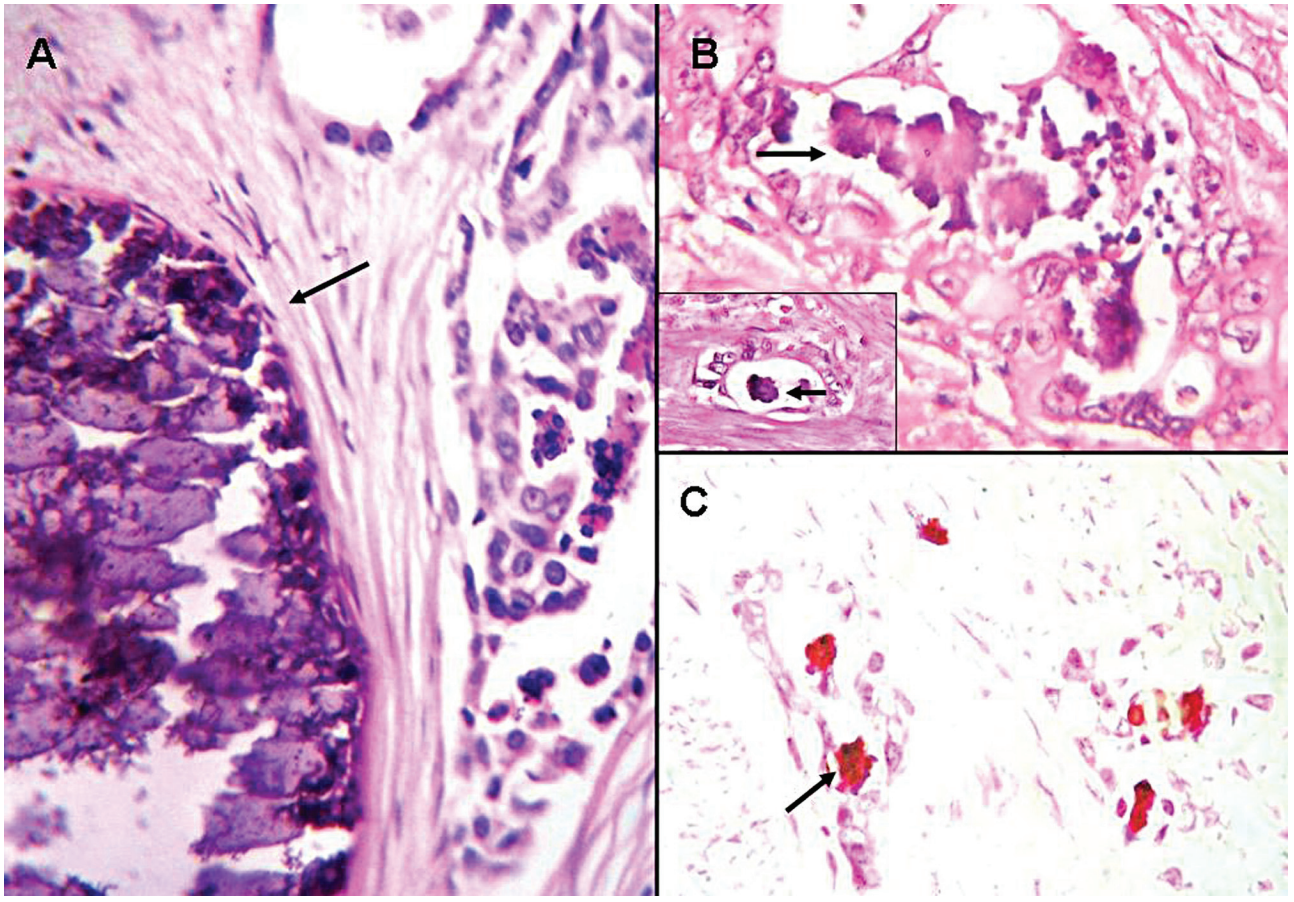

Figure 1. A: Course calcification in glandular lumen *(arrow)* in moderately differentiated non-mucinous adenocarcinoma (Case 1). **B**: Psammomatous calcification in gastric adenocarcinoma *(arrows)*. **C:** von Kossa stain *(arrow)* in psammomatous calcification.

rent case (Case 1) is another cause of increased stomach pH and may therefore cause calcification (20). Although calcification in gastric carcinomas may be detected by plain X-ray of the abdomen, barium study, CT scan, and conventional ultrasound (19,24) particularly in diffuse calcification, demonstrating psammomatous calcifications by these conventional imaging devices is often difficult due to their small size and requires advanced techniques including endoscopic ultrasonography (25). In both of the presented cases, CT and X-ray findings were all unremarkable.

Whatever the cause, it remains controversial as to why some gastric cancers calcify while most do not. On the other hand, it is evident from the literature that calcium-producing mucinous gastric cancers cause only diffuse calcification and not psammomatous (10,16,17,19,24,26). In the English literature, diffuse calcification has not been reported in non-mucin-producing intestinal gastric carcinoma. To our knowledge, Case 1 represents the first such case.

The exact mechanism involved in psammoma body formation in intestinal type gastric carcinoma has not been elucidated (13,16), although ultrastructural studies have suggested intracytoplasmic origin (16). However, psammoma bodies may originate from necrotic or degenerating tumor cells after a crystal nidus is formed in the lumens of the glands (1,2). Correspondingly, psammoma bodies as well as accompanying hyaline globules seen in some cases of gastric adenocarcinomas were considered as degenerative changes of neoplastic cells by some authors (11). It has been suggested that psammomatous calcification in meningioma and desmoid tumor is a result of direct mineralization of round, whorled collagen bodies, which have been suggested as the precursor lesion of psammoma bodies (27,28). It has also been proposed that the initial foci of mineralization in psammoma bodies are extracellular matrix vesicles derived from cellular degeneration with hydroxyapatite within matrix vesicles by ultrastructural study of psammoma bodies in meningocytic whorl (29). Mitochondria ha-

Table 1. Reported cases of intestinal type gastric carcinoma with psammomatous calcification

Author	Age	Sex	Location	Psammoma bodies	
				Primary	Metastasis
Yasuma et al. (25)	45	F	Antrum	(+): G	(-)
Imai et al. (17)	62	M	GEJ	(+): G & S	(+): LN
Murayama et al. (16)	62	M	Pyloantrum	(+): G	(-)
Niwa et al. (15)	51	M	GEJ	(+): G	(-)
Park et al. (13)	49	M	Prepyloric antrum	(+): G	(-)
Kawahara et al. (14)	82	F	GEJ (remnant stomach)	(+): G	(-)
Present case (Case 2)	54	F	Cardia-corpus	(+): G	(-)

F: Female. M: Male. GEJ: Gastroesophageal junction. G: Gland. S: Stroma. LN: Lymph node.

ve been considered then as the initial focus of intracytoplasmic calcification (28). However, ultrastructural observation of needle-like crystalline deposits other than mitochondrial calcification was made by several investigators, particularly in papillary carcinoma of the endometrium, duodenal carcinoma and non-mucinous carcinoma of the stomach (6,16,30,31).

Osteopontin protein produced by macrophages has been reported to play a significant role in the development of psammomatous and non-psammomatous calcification in human neoplasms (13,14, 32,33). Psammomatous calcification was also found to produce a parathyroid hormone (PTH)-like substance, suggesting a potential role in the pathogenesis of the psammomatous calcification (16). Metastatic calcification is theoretically feasible in cases with persistent hypercalcemia (13). Thus, PTH-producing tumors may cause metastatic calcification (34). Murayama et al. (16) reported that a high level of PTH-like substance was noted in the tissue extract of their gastric carcinoma with psammomatous calcification, but serum calcium level and PTH were normal and the mechanism of calcification was different from metastatic calcification. Bone morphogenetic protein may be another potential contributor in the formation of psammoma bodies (14).

Psammomatous calcification is generally observed in the lumina of gastric cancer, and rarely in tumoral stroma, but not in non-neoplastic tissues adjacent to the tumor (15). In contrast to diffuse calcification occurring within the pools of mucin in mucinous gastric carcinoma (17), psammoma bodies are extremely rare in gastric carcinoma, with only six published cases (13-17,25). Case 2 reported herein is the seventh such case. All cases with psammomatous calcification including the present case are summarized in Table 1. All tumors were non-mucin-producing intestinal type adenocarcinomas with psammoma bodies in gland lumens. The case reported by Imai et al. (17) displayed some unique features: there were stromal psammoma bodies as well as those in glandular lumens, and psammoma bodies were present both in primary cancer and in metastatic lymph nodes.

It has been proposed that patients with mucinous gastric cancer showing diffuse type of calcification are relatively young in age and probably have a better survival than those gastric cancer cases without calcification (18). However, it is unclear whether the calcification type –diffuse or psammomatous - is important due to the limited number of cases with psammomatous calcification. In serous adenocarcinoma of the ovary, a significantly higher survival rate has been found in cases with psammoma bodies than in those without. However, the presence and number of psammoma bodies are not statistically significant prognostic indicators in papillary carcinoma of the thyroid (35). Therefore, the significance, if any, of calcification, particularly psammomatous type, in gastric adenocarcinoma remains undetermined.

In conclusion, calcification of gastric cancer is an uncommon but interesting entity. Each case should be reported in detail to conceive a comprehensive data and to determine its pathogenetic mechanisms as well as prognostic significance.

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