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EDITORIAL

Lymph node, peritoneal and bone marrow micrometastases in gastric cancer: Their clinical significance

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Abstract

The 7th TNM classification clearly states that micrometastases detected by morphological techniques (HE stain and immunohistochemistry) should always be reported and calculated in the staging of the disease (pN1mi or M1), while patients in whom micrometastases are detected by non-morphological techniques (e.g., flow cytometry, reverse-transcriptase polymerase chain reaction) should still be classified as N0 or M0. In gastric cancer patients, micrometastases have been detected in lymph nodes, the peritoneal cavity and bone marrow. However, the clinical implications and/or their prognostic significance are still a matter of debate. Current literature suggests that lymph node micrometastases should be encountered for the loco-regional staging of the disease, while skip lymph node micrometastases should also be encountered in the total number of infiltrated lymph nodes. Peritoneal fluid cytology examination should be obligatorily performed in pT3 or pT4 tumors. A positive cytology classifies gastric cancer patients as stage Ⅳ. Although a curative resection is not precluded, these patients face an overall dismal prognosis. Whether patients with a positive cytology should be treated similarly to patients with macroscopic peritoneal recurrence should be evaluated further. Gastric cancer cells are detected with high incidence in the bone marrow. However, the published results make comparison of data between groups almost impossible due to severe methodological problems. If these methodological problems are overcome in the future, specific target therapies may be designed for specific groups of patients.

Key words: Gastric cancer; D2 lymphadenectomy; Lymph node micrometastases; Peritoneal micrometastases; Bone marrow micrometastases

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INTRODUCTION

Histologically confirmed metastatic infiltration of peri- and extra-gastric lymph nodes has been defined as the strongest independent dismal prognostic factor for both early[1] and advanced[2] gastric cancer patients. It could be proposed that, by performing a D2 lymphadenectomy, coexisting micrometastases, skip metastases and skip micrometastases are resected and thus more R0 resec-

tions are achieved, facts probably leading to locoregional control of the disease, better outcome and increased survival[3,4].

However, recurrences are very common, even after an oncological R0 resection, and the peritoneum represents the most frequent site of recurrence of the disease[5]. This fact is probably related to the intraperitoneal presence of free cancer cells shed from the serosal surface of the primary tumor[6]. It is uniformLy accepted that peritoneal metastasis constitutes the most frequent cause of death, with a mean survival of only a few mo following peritoneal recurrence[7].

Moreover, even after an aggressive surgical approach and extended lymphadenectomy, a significant proportion of patients will eventually develop metastatic disease despite the potentially curative surgery, indicating the presence of early disseminated disease not apparent at the time of primary treatment. Since epithelial cells are not present in bone marrow under normal circumstances, identification of micrometastases in the bone marrow has been proposed as evidence of systemic micrometastatic disease[8]. It is likely that this group of patients is under staged, probably because of the presence of occult metastatic disease at the time of initial surgery[9].

The 7th TNM classification[10] defines micrometastases as a metastatic focus between 0.2 and 2 mm and clearly states that, if they are detected by morphological techniques (HE stain and immunohistochemistry), they should always be reported and calculated in the staging of the disease (pN1mi or M1). On the other hand, patients in whom micrometastases are detected by non-morphological techniques [e.g., flow cytometry, reverse-transcriptase polymerase chain reaction (RT-PCR)] should still be classified as N0 or M0. Obviously, the previously mentioned terminology, classification and clarifications can also be applied in gastric cancer.

Herein, we review the current knowledge and evidence of the prognostic significance of lymph node, peritoneal and bone marrow micrometastases detectable by morphological techniques in gastric cancer patients.

LYMPH NODE MICROMETASTASES

Three methods have been used for the identification of lymph node micrometastasis: serial sectioning, immunohistochemical staining and RT-PCR. Serial sectioning constitutes a histological method, which can detect metastasis previously missed by the conventional technique, but may still fail to identify isolated tumor deposits[11]. RT-PCR has been reported as highly sensitive[12] but it is compromised by false-positive results caused by biological contamination[13]. Positive RT-PCR results indicate the presence of tumor DNA; however, they may not indicate the presence of viable tumor cells[14]. Thus, immunohistochemistry with human anti-CK antibodies represents the most accurate method for micrometastasis detection[15] and the most frequently applied technique in research[16].

Lymph node micrometastases have been reported as immunohistochemically detectable in 10% of early gastric cancer patients[16], in 52.6% of T2N0 patients[17], and in 21%[18] to 49%[19] of all node-negative gastric cancer patients.

Particularly in the subgroup of level I lymph node negative patients, the incidence of histologically detected metastases in the level Ⅱ lymph nodes (skip metastases) ranges between 2.8% in cases of early[20] and 5%[21] to 17.4%[22] in all other gastric cancers. Moreover, in patients who had been histologically classified as level I lymph node negative, the incidence of micrometastases detected by immunohistochemistry in the level Ⅱ lymph nodes (skip micrometastases) ranges between 10% in cases of early[23] and 17%[24] in cases of T1-2N0 gastric cancers.

Although other reports[25,26] failed to show any relationship between micrometastases presence and recurrence rate or outcome, Cai *et al*[27] reported a 5 years survival of 100% for the micrometastasis negative, compared to an 85% for the micrometastasis positive *sm* gastric cancer patients. Maehara *et al*[28] reported a 50% shorter survival for the micrometastases positive, compared to the micrometastases negative, early gastric cancer patients who died from recurrence of the disease. Saito *et al*[29] reported the presence of micrometastases in 50% of the early gastric cancer patients who presented with recurrence of the disease classified as pN0 on the initial conventional histology. Finally, experimental data[30] addressed that micrometastases in lymph nodes have high proliferative activity, thus potentially can develop metastases. Based on the above, micrometastases undoubtedly cannot be ignored.

The clinical significance of the skip metastases and skip micrometastases remains controversial and the controversies are mainly related to the small number of patients enrolled in skip metastasis studies[31], the probable different prognosis of patients with histologically *vs* micrometastatically detected skip metastases[15] and the concern that patients with histologically detected skip metastasis may represent cases of overlooked histological metastasis or micrometastasis in level I lymph nodes, thus being misclassified as patients with skip metastasis[32].

Saito *et al*[32] compared gastric cancer patients with skip metastasis to patients with metastasis in the level I and level Ⅱ lymph nodes and concluded that both the clinicopathological characteristics as well as the prognosis of patients with skip metastasis were similar to patients with level I lymph node metastases, but not to patients with level Ⅱ lymph node metastases. Li *et al*[22] reported that the cumulative survival rate was not statistically different between gastric cancer patient with solitary skip lymph node metastases compared to patients with solitary level I lymph node metastases. Park *et al*[31] reported that in patients with positive nodes extending into the level Ⅱ lymph nodes, the survival curves did not show statistical differences between skip(+) and skip(-) groups of patients, further supporting the theory that the number but not the level of lymph node metastases has prognostic significance.

A last issue regards the clinical significance of the possible micrometastatic infiltration of the nos 7 and 9 lymph node stations complex. It has been proposed that the most likely route for para-aortic lymph node metastases is from the left gastric artery nodes, passing by the celiac artery[33]. Thus, these lymph nodes should be always evaluated, regardless the mode of operation, even in cases of minimally invasive surgery. Yanagita *et al*[34] investigated the clinical significance of the morphological distribution of metastatic foci (metastasis, micrometastasis or isolated tumor cells) in sentinel lymph nodes with gastric cancer and concluded that in patients with non-marginal sinus type sentinel node metastasis, attention should be paid to the possibility of non sentinel node or even pN2 metastases presence. Thus, if the sentinel node cannot be identified in the perigastric lymph nodes, around the celiac artery lymph nodes should be always explored to reduce the likelihood of false negative results in sentinel node mapping[20].

PERITONEAL MICROMETASTASES

It has been postulated that the majority of gastric cancer patients with intraperitoneal free cancer cells (IFCCs) do not escape postoperative peritoneal recurrence[35]. For more than three decades, IFCCs have been assumed to play an important role in the development of peritoneal metastases, which is the foremost pattern of failure after potentially curative resection for gastric cancer[6,36-40], while the peritoneal cavity can be a route for dissemination of malignant cells, either by direct continuity with the lesion or acting as a receptacle for lymphatic spread[38,40].

Peritoneal lavage cytology is widely accepted as the gold standard for diagnosis of IFCCs. Upon entering the abdominal cavity, prior to manipulating the tumor, 200 mL of warm normal saline is introduced and manually dispersed in the Douglas cavity, paracolic gutters and in the right and left subphrenic cavity. At least 50 mL of fluid is subsequently recovered, after gentle stirring, from several regions of the abdominal cavity. The fluid is then centrifuged for 5 min at 1500 r/min. The sediment is smeared onto one or more glass slides and stained using Papanicolaou's method. Cytological findings are classified as positive, negative or suspicious. The following cell characteristics are used to determine the presence of malignant cells: presence of aggregate, size, shape, type of cytoplasm, cytoplasmic vacuoli, mainly nuclear abnormalities, nuclear chromatin, nuclear-cytoplasmic ratio, mitotic figures and nucleolar prominence. When necessary, the glass slide containing the nucleated cell layer is further analyzed by immunohistochemistry using the CEA antigen antibodies[41].

Cytology can be easily and safely performed; it requires approximately 15 min for a cytopathologist to analyze the patient's slides and its estimated cost is $60.20[42]. The method has a sensitivity of 90% to 96.7% and nearly 100% specificity in the diagnosis of IFCCs[43]. False-positive results have been recognized with a rate of 4.5% to 5%, probably secondary to reactive mesothelial cells[38,39,44], but this problem can be eliminated by the use of immunohistochemistry[45].

The detection rate of IFCC ranges between 14% and 47%, depending upon the cohort of patients included[6,35-40,44], while, when only potentially curative resections were included, the rate of IFCC varied from 4.4% to 11%[46-48], and from 22% to 30% in gastric carcinoma involving the serosa[49,50].

Mezhir *et al*[51] demonstrated that a positive peritoneal cytology, even in the absence of gross peritoneal disease, indicates a poor outcome. In the Dutch Gastric Cancer Group[48], positive cytological findings were found in 4.4% of the patients and were indicative of a poor prognosis, with a median survival of 13 mo. In Bentrem *et al*'s study[46], which included 371 patients with gastric carcinoma undergoing diagnostic laparoscopy and peritoneal washing cytology prior to any attempt for R0 resection, IFCCs were detected in 6.5% of the patients and this finding was an independent dismal prognostic factor, correlating with a median survival of 14.8 mo *vs* 98.5 mo for patients with negative cytology. Thus, the Japanese Society for Gastric Cancer has included peritoneal cytology as part of the staging procedure[52], while the TNM classification system has classified cytology-positive gastric cancer patients as stage Ⅳ patients since 1997[53].

In cases of gross peritoneal recurrence, the promising results which have been reported[54,55] following cytoreductive surgery and intraperitoneal chemotherapy suggest that an aggressive approach to the peritoneum may improve survival. However, randomized studies examining the effectiveness of cytoreductive surgery and intraperitoneal chemotherapy as a standard treatment strategy in select patients with peritoneal carcinomatosis from gastric cancer are required[54]. On the other hand, the management of patients with positive peritoneal cytology as the only evidence of M1 disease is largely unknown[50,51,54]. However, results from Western series suggest that a positive peritoneal cytology is related to a poor outcome regardless of treatment[46,56].

BONE MARROW MICROMETASTASES

Several studies in upper gastrointestinal tract cancer patients disclosed the presence of bone marrow micrometastases, both in the preoperative period as well as up to twelve mo after surgery. When micrometastases are detected preoperatively, some do not persist and may represent transient shed cells that the host can clear[57]. For micrometastases detected at the time of surgery, it is believed that these tumor cells represent systemic residual disease, while single clonogenic tumor cells are the reason for later clinical relapse[58].

Bone marrow micrometastases do not represent "true" micrometastases based on the TNM terminology. However, in gastric cancer patients, the incidence of epithelial cells detected by immunohistochemistry at the time of the curative resection in the bone marrow of the iliac crest

ranges between 25%[59] and 53%[60], although tumor cells appear more frequently (79%) in resected rib marrow[61].

Compared to clinicopathological factors of the primary tumor, bone marrow micrometastases have been reported to be related to the depth of invasion of the gastric wall, cytological differentiation, lymph node spread and increased tumor microvessel density[62].

The clinical or the prognostic significance of bone marrow micrometastases are still a matter of debate. Schlimok *et al*[63] found that epithelial cells were detectable in the bone marrow of 35% of gastric cancer patients without distant metastases and, in univariate analysis, their presence has adverse prognostic significance for the relapse-free survival. Jauch *et al*[60] found that epithelial cells were detectable in the bone marrow in 53% of gastric cancer patients without distant metastases and, in multivariate analysis, the presence of three or more cells had adverse prognostic significance for disease free survival for patients with T1-2N0 tumors while it did not reach significance for more advanced tumors or for patients with less than three epithelial cells in bone marrow. Heiss *et al*[58] concluded that a high expression of plasminogen activator inhibitor type 1 in tumor cells in bone marrow represents an independent dismal prognostic factor for the disease free survival of T1-2 tumors. On the other hand, Schott *et al*[64] and de Manzoni *et al*[65] clearly stated that the presence of cytokeratine-positive cells in the bone marrow of curatively resected gastric cancer patients did not affect outcome. However, bone marrow micrometastases in the rib were detected in 67% of esophagogastric cancer patients treated with surgery alone, but only in 39% of post-neoadjuvant chemoradiotherapy patients[66].

The inconsistency among the previously mentioned reports can be explained either by methodological problems related to the immunohistochemical techniques or by the clinical behavior of the gastric cancer itself.

All authors agree that the published results make comparison of data between groups almost impossible due to severe methodological problems such as: the lack of consensus about the preferable detection method; the lack of standardization of the methods used; whether immunohistochemistry was chosen as the method of choice and cytokeratins as the optimal antigens; the selection of the antibody; the number of cell analyzed; and the selection of the control specimens which can all influence the results. Finally how many cells are needed in order establish a positive result needs to be clarified[67].

Unlike the hypothesis that the contact of gastric cancer cells with peritoneal cells supports their ability to develop the full metastatic phenotype, cancer cells in the bone marrow might have been positively selected during early stages of metastasis and the majority of these cells appear to be in a dormant state of cell growth[68].

CONCLUSION

A D2-lymphadenectomy specimen should always be evaluated for detection of lymph node micrometastases, which should be further encountered in the loco-regional staging of the disease. The detection of skip lymph node micrometastases should also be encountered in the total number of infiltrated lymph nodes. If there is a suspicion of gastric serosa invasion (pT3 or pT4), peritoneal fluid cytology examination should be obligatorily performed in order to verify the presence of IFCCs. A positive cytology classifies gastric cancer patients as stage IV, indicating a poor prognosis even for those who underwent a potentially curative resection. Whether patients with a positive cytology should be treated similarly to the patients with macroscopic peritoneal recurrence should be evaluated further. Since the prevalence of gastric cancer cells in the bone marrow is high, neoadjuvant or adjuvant therapies should not be precluded in selected groups of patients. Which patients will be classified as high-risk should be determined by future studies. If a uniformly accepted methodological technique for bone marrow micrometastases detection is established in the future, specific target therapies may be applied in specific groups of patients.

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CASE REPORT

Simultaneous intraductal papillary neoplasms of the bile duct and pancreas treated with chemoradiotherapy

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Abstract

Some authors have suggested that intraductal papillary mucinous neoplasms of the bile duct (IPMN-B) could be the the biliary counterpart of IPMN of the pancreas (IPMN-P) since they share several clinical-pathological features. These include prominent intraductal papillary proliferation pattern, a gastrointestinal phenotype, frequent mucin hyper-secretion and progression to mucinous carcinoma. To date there are just four reported cases of patients with synchronous IPMN-B and IPMN-P all of which were treated surgically. We hereby report the case of a 76-year-old woman who was incidentally diagnosed with both an asymptomatic 3 cm bulky fluid lesion obstructing the bile duct lumen, diagnosed as a malignant IPMN-B, and synchronous multiple pancreatic cystic lesions (10-13 mm) communicating with an irregular Wirsung, diagnosed as branch duct IPMN-P. Since surgery was ruled-out because of the patient's age and preferences, she underwent a conservative management regimen comprising both chemotherapy and radiotherapy. This was effective in decreasing the mass size and in resolving subsequent jaundice. This is also the first reported case of IPMN-B successfully treated with chemoradiotherapy. Clinicians should consider medical treatment as an option in this clinical scenario, in patients who may be unfit for surgery.

Key words: Intraductal papillary neoplasm; Bile duct; Simultaneous; Pancreatic intraductal papillary mucinous neoplasm

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INTRODUCTION

Intraductal papillary mucinous neoplasms of the pancreas (IPMN-P) are lesions generally characterized by proliferation of the mucinous epithelium with vary degrees of ductal and cystic dilatation[1,2]. By definition, these tumours reside within the main pancreatic duct or its side branches and frequently manifest with grossly visible papillary growths producing mucin.

Depending on their location within the pancreatic ductal system, they are subclassified as branch duct IPMN, main duct IPMN, or combined-IPMNs, the latter being characterized by the involvement of both the main pancreatic duct and the branch-ducts. The reported 5-year risk of developing high grade dysplasia or invasive carcinoma is directly related to this localization with a risk exceeding 70% for tumours arising from the main duct, and substantially lower (25%) risk for lesions of the branch ducts[3,4].

Accordingly, surgery has been indicated for patients with main duct IPMN-P, for branch duct lesions of size > 30 mm or when particular features, such as nodules or thick walls, as present[5].

The clinical behaviour of IPMN-P is less aggressive than pancreatic adenocarcinoma, even when the lesion shows malignant features. The overall 5-year survival rate is indeed higher in patients with malignant invasive IPMN than in those with pancreatic ductal carcinoma (36% *vs* 21%)[6].

In the past few years a rare subtype of cholangiocarcinoma, which shows a mainly papillary proliferation into the bile duct lumen, has been identified and classified as papillary cholangiocarcinoma. The term intraductal papillary mucinous neoplasms of the bile duct (IPMN-B) has also been employed for this tumour type, as it shares some histopathologic and clinical aspects with IPMN-P. Indeed, IPMN-B seem to have a better clinical prognosis than the other major types of cholangiocarcinoma[7], with a reported 5-year survival rate for IPMN-B after surgical resection close to 38%[8]. However, most reported cases or series of IPMN-B have been treated surgically, and the possible role of medical treatments in patients with IPMN-B has not been investigated.

Interestingly, a few cases of IPMN-B and IPMN-P occurring simultaneously have been reported[9-12], possibly suggesting a common carcinogenesis pathway.

As all reported cases of simultaneous IPMN-B and IPMN-P were also treated surgically, the possible outcome of such patients when managed conservatively is unknown. We hereby report a case in which IPMN-B and IPMN-P were diagnosed, simultaneously and incidentally, in a patient who received chemoradiotherapy, with excellent results in long-term follow-up.

CASE REPORT

A 76-year-old woman, with a history of hypertension, hypercolesterolemia and type II diabetes was incidentally diagnosed with an asymptomatic mass in the liver during routine abdominal ultrasonography (US) performed for evaluation of haematuria. She subsequently underwent abdominal computer tomography (CT) scan and magnetic resonance imaging, resulting in the identification a 25 mm × 18 mm intrahepatic cholangiocarcinoma. Moreover, both imaging modalities disclosed the presence of multiple pancreatic cystic lesions (ranging 10-13 mm) located in the uncinate process and in the tail of the pancreas.

The patient was referred to our Centre 3 mo after the initial US, and a magnetic resonance cholangiopancreatography (MRCP) was performed. This demonstratied a 30-mm bulky fluid lesion, with a 25-mm endoluminal solid component, occupying the bile duct lumen in the right liver, as well as multiple pancreatic cystic lesions (ranging 10-13 mm) in the uncinate process and in the tail of pancreas and communicating with an irregular Wirsung, consistent with the diagnosis of diffuse branch duct pancreatic IPMN. Endoscopic ultrasound (EUS) confirmed the presence of an hepatic irregular fluid lesion originating from the bile duct (major diameter 23 mm) with an internal solid component, and multiple dilatations in both the uncinate process and of in the tail of the pancreas, suggestive for branch duct IPMN-P. However, an EUS-guided fine needle aspiration of the biliary lesion was inconclusive for cancer cells. At that time the patient was asymptomatic, the carbohydrate antigen 19-9 levels were normal and there was no biliary tract dilatation or biochemical abnormalities. The possibility of surgery was discussed with the patient, who refused this option and a follow-up was programmed.

Seven months later a follow-up MRCP demonstrated disease progression (Figure 1A) with an increased size of the bile duct lesion (40 mm), which now extended to the biliary confluence. Its content was described as a fluid proteic component consistent with mucin. The pancreatic lesions were stable. Blood tests showed initial signs of cholestasis [aspartate transaminase 331 U/L (n.v 15-46 U/L), alanine transaminase 273 U/L (n.v 11-66 U/L), γ glutamyl transferase 476 U/L (n.v 8-78 U/L), alkaline phosphatase 161 U/L (n.v 35-128 U/L)]. An endoscopic retrograde cholangiopancreatography (ERCP) was performed and a biliary plastic stent (10 FR) was inserted. Multiple endoscopic bioptic and brushing assays on the biliary lesion indicated biliary duct cells with a papillary growth, showing severe dysplasia and cancer foci, within lakes of mucin. The findings were considered suggestive for an invasive IPMN-B.

Given the patient's preferences, age and co-morbidities, a conservative management was chosen and the patient underwent concomitant chemotherapy (5-fluoruracine, 5 d infusion for 6 wk 225 mg/m^2 per die) and radiotherapy (total 50.4 Gy; 1.8 Gy/28 fractions, for 6 wk).

Three months after the end of the treatment (18 mo after the diagnosis) she underwent a re-staging CT-scan and a MRCP which showed a decrease in the size of the biliary lesion (30 mm) and a prevalence of the endoluminal component (Figure 1B), and an absence of bile duct dilation. The pancreatic lesions were again stable in size. As the patient was asymptomatic and blood tests in the

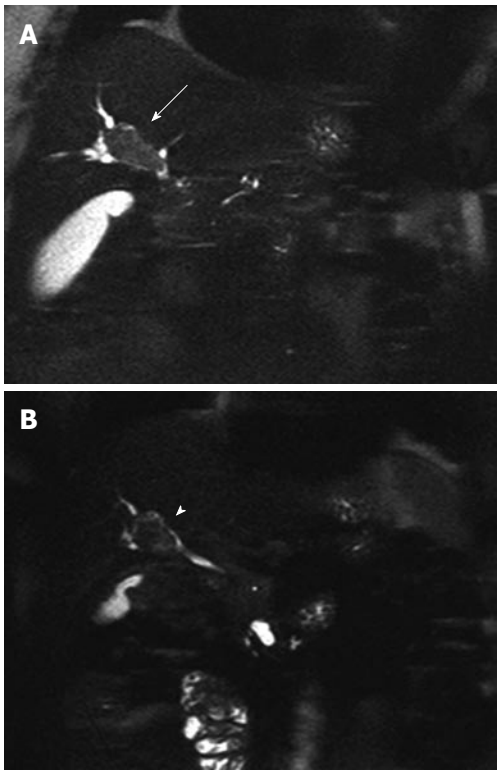

Figure 1 Haste in coronal plane. A: Biliary lesion (40 mm in size) extending to the biliary confluence (arrow); B: A reduction of the biliary lesion (30 mm in size) after radio-chemotherapy with a prevalence of the endoluminal component, in the absence of bile duct dilatation (arrowhead).

normal range, a new ERCP was performed and the plastic biliary plastic was removed.

Five months later (23 mo after the diagnosis) a new MRCP again showed signs of disease progression, with an increase in the size of both the biliary (45 mm) and of the largest pancreatic lesions (31 mm). This increase in size of > 1 cm in few months, with a lesion size exceeding 3 cm is considered to be suggestive of a potentially malignant behaviour[2,13]. A second EUS confirmed the presence of the biliary lesion extending from the median third of the main biliary duct to the hepatic hilum, and of multiple pancreatic lesions communicating with a dilated Wirsung's duct. EUS-FNA of the largest cystic pancreatic lesion (Figure 2) in the uncinate process was performed and fluid collected for further analyses. The cystic fluid level of Carcinoembryonic Antigen (CEA) was 27 U/L and amylase was 23.8842 U/L. Cytological examination showed dysplastic epithelium within lakes of mucin.

The patient then underwent second-line chemotherapy treatment (Gemcitabine 1000 mg/m^2, 1,8,15 q28, 3/4 wk).

A restaging CT-scan 28 mo after diagnosis showed a new stabilization, of both the biliary (45 mm) and of the pancreatic lesions. This was further confirmed by another MRCP conducted 3 mo later (31 mo after the diagnosis), which demonstrated a significant decrease in size of the major pancreatic lesion (20 mm).

Currently (36 mo after the diagnosis) the patient is asymptomatic and in good clinical conditions, the disease is stable, and she is undergoing her 26th administration of chemotherapy.

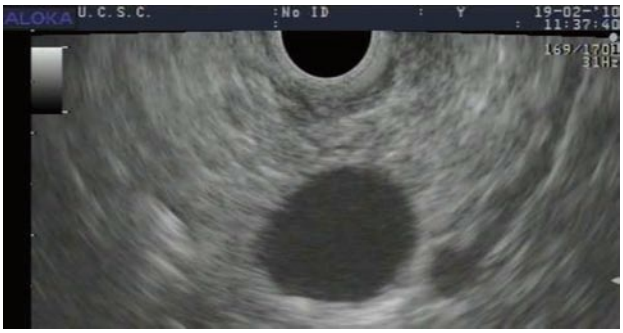

Figure 2 Ultrasound endoscopy image of the pancreatic lesion in the uncinate process showing a 30-mm anechoic lesion without any solid nodule or solid component.

DISCUSSION

We have described a case of concomitant biliary and pancreatic IPMNs that were diagnosed incidentally and were managed conservatively by endoscopic stent placement and chemo-radiotherapy with a good clinical outcome in a 3-year follow-up.

The term biliary IPMN refers to a recently classified subtype of cholangiocarcinoma, which is considered the biliary counterpart of pancreatic IPMN, as they share several clinico-pathological features. These include a prominent intraductal papillary proliferation pattern, a gastrointestinal phenotype, frequent mucin hyper-secretion and progression to mucinous carcinoma[8,14].

Such intraductally-growing tumours account for only a small fraction of cholangiocarcinomas, and represent an equivocally-classified entity that has been described in the literature with several different names (mucin-producing intrahepatic cholangiocarcinoma, biliary papillary tumor, mucin producing bile duct tumor, intrahepatic biliary intraductal papillary mucinous neoplasia, IPMN-B, biliary IPMN)[15].

IPMN-Bs present with striking similarities to pancreatic IPMNs, including intraductal papillary growth, the production of mucin and the relatively indolent clinical behaviour. As the biliary tract and the pancreas have a common embryologic origin from the ventral foregut, it seems plausible that some common genetic events may lead to the development of IPMN-P and IPMN-B.

Interestingly, it has recently been proposed that only IPMN-Bs with proper mucin production, such as the one diagnosed in the present report, share histopathological and molecular similarities with IPMN-P[16], and that although the clinicopathological features of IPMN-B resemble those of IPMN-P, the biliary lesions have a higher malignancy rate[17].

To the best of our knowledge, there have been only four reported cases of patients with synchronous IPMN-B and IPMN-P, all of which weresurgically treated[9-12]. We

have made the first presentation of the clinical course of a case treated conservatively with a good clinical outcome in a long-term follow-up. This suggests that even in aggressive cases, with clear signs of malignant transformation, concomitant IPMN-B and IPMN-P may be conservatively managed with chemoradiotherapy in patients with a relatively high surgical risk.

Intraductal papillary mucinous neoplasms of the pancreas are being increasingly diagnosed due to improved imaging techniques and greater awareness[18]. Therefore, their incidental diagnosis often occur in elderly patients undergoing imaging procedures for other disorders[19,20]. In such cases, surgery may be ruled-out, even in presence of factors associated with a higher risk of malignancy.

However, there have been no reported studies specifically investigating the possible efficacy of chemotherapy and/or radiotherapy in this setting. Our finding of a radiologic response of both biliary and pancreatic intraductal papillary mucinous neoplasms to medical treatments may therefore prove interesting for similar cases, in the absence of evidence from clinical trials.

On the other hand, whether the coincidence of these two neoplasms is merely accidental, or part of a defined phenotype requires further detailed clinical and molecular studies on larger series.

Our observation seems to confirm that IPMN-B and IPMN-P, even when occurring simultaneously and with signs suggesting a malignant behaviour, have a relatively good prognosis and require a specific multidisciplinary therapeutic approach.

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CASE REPORT

Running in the family: MALT lymphoma and autoimmune disease in mother and daughter

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Abstract

Gastric B-cell lymphoma of the mucosa associated lymphoid tissue (MALT) lymphoma is one of the most common forms of extranodal lymphoma. In addition to infection with *Helicobacter pylori* (*H. pylori*), the presence of an underlying autoimmune disease has also been associated with MALT lymphoma development. To date, no familial predisposition for MALT lymphomas has been reported as opposed to other types of lymphoma. A 65-year-old woman was admitted at our institution in 1998 with a diagnosis of *H. pylori* positive gastric MALT lymphoma and the presence of chronic autoimmune thyroiditis was established on further work-up. *H. pylori* eradication did not result in regression of the lymphoma and RT-PCR showed the presence of the t(11;18)(q21;q21) translocation. About 1.5 years after *H. pylori* eradication, chemotherapy with cladribine resulted in complete remission. Due to lymphoma recurrence 13 mo later, radiotherapy to the stomach (46 Gy) resulted in minimal residual disease without further progression. The patient developed a second malignancy (Epstein-Bar virus-associated anaplastic large cell lymphoma in the mediastinum) in 2004 which initially responded to two courses of chemotherapy, but she refused further therapy and died of progressive lymphoma in 2006. In 2008, her 55 years old daughter with a long standing Sjögren's syndrome was diagnosed with MALT lymphoma of the right parotid, but no evidence of gastric involvement or *H. pylori* infection was found. Currently, she is alive without therapy and undergoing regular check-ups. To our knowledge, this is the first report of MALT lymphoma in a first-degree relative of a patient with gastric MALT lymphoma in the context of two autoimmune diseases without a clearly established familial background.

Key words: Mucosa associated lymphoid tissue lymphoma; *Helicobacter pylori*; Autoimmunity; Familial lymphoma

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INTRODUCTION

Malignant lymphomas are tumors with an increasing incidence. Despite wide geographic variations, the overall incidence is currently estimated at 2/100 000[1]. As opposed to solid tumors, however, malignant lymphomas constitute a heterogeneous group of different disease entities. In view of this, an explanation for the rising incidence

is difficult, as various types of lymphomas have distinct characteristics and contributing pathogenetic factors. In general, the presence of an autoimmune disease has been judged to be risk factor for the development of malignant lymphomas and Sjögren's syndrome (SS), rheumatoid arthritis, autoimmune thyroiditis and Lupus erythematosus have especially been associated with the development of diffuse large B-cell lymphomas, extranodal marginal B-cell lymphomas of the mucosa associated lymphoid tissue (MALT lymphoma), but also Hodgkin's disease[2-4]. Controversially, immunosuppression has also been linked to lymphoma development, as evidenced by patients with post-transplant lymphoproliferative diseases and patients being given immunosuppression for rheumatoid diseases. In the latter, however, there is still some controversy as to whether lymphoma development is de facto linked to the underlying disease necessitating immunosuppression rather than the immunosuppressive agents[5,6].

A familial background of non-Hodgkin's lymphoma (NHL) has repeatedly been reported to constitute a significant risk factor for lymphoma development. In an evaluation of first-degree relatives of lymphoma patients, Paltiel *et al*[7] observed an increased rate of both NHL as well as Hodgkin's lymphoma development among the population when compared to control groups. The Swedish Family Cancer database analyzed familial risk for NHL in terms of histopathological subtypes and showed a significantly increased risk for diffuse large B-cell lymphomas and follicular lymphomas[8].

MALT lymphoma is among the more common lymphoma subtypes and constitutes about 7%-8% of all newly diagnosed B-cell lymphomas[9]. In terms of pathogenesis, gastric MALT lymphoma is the paradigm for an immunomediated malignancy, as evidenced by the strong association with SS, autoimmune thyroiditis and, in case of gastric MALT lymphoma, infection with *Helicobacter pylori* (*H. pylori*)[10]. The validity of the latter model/association has been demonstrated by the impressive response of gastric MALT lymphomas to eradication of the bacteria, resulting in complete remissions in up to 80% of selected patients[11,12]. Apart from autoimmunity and chronic antigenic stimulation driven by infections, however, no risk factors for MALT lymphoma have been reported, and no evidence for familial clustering of MALT lymphomas can be found in the current literature.

We report the cases of two women (mother and daughter), who both developed MALT lymphoma with the background of an autoimmune disease.

CASE REPORT

A 65-year-old woman was admitted at our institution for further treatment of a recently diagnosed gastric MALT lymphoma in September 1998. Due to epigastric complaints for a period of about five mo, a gastroscopy was performed, which disclosed the presence of a gastric ulcer in the corpus. Multiple biopsies from the ulcer as well as from the surrounding hyperemic mucosa were taken, and disclosed the presence of extranodal marginal zone MALT lymphoma along with active infection with *H. pylori*. Antibiotic therapy with clarithromycin, metronidazole for 10 d and intake of pantoprazole were initiated. At our institution, a re-gastroscopy was performed 6 wk after eradication therapy, showing no evidence of *H. pylori* and healing of the ulcer, but unchanged histological presence of MALT lymphoma. RT-PCR performed on paraffin embedded specimens showed the presence of the MALT lymphoma specific t(11;18)(q21;q21)-translocation.

The patient's initial physical condition was good and blood counts were normal except an elevated β2-microglobulin level (2.73 mg/L) and anemia grade I related to slight chronic blood loss from the gastritis. The medical history revealed appendectomy, cholecystectomy and hysterectomy and the familial history was positive for malignancies (mother died age 38 years from what the patient related as "acute leukemia" and a brother had died from pancreatic carcinoma). At the time of admission, the medical history of both the patient's daughters was uneventful, except SS in the older daughter which had been histologically verified in 1993. Extensive staging including endosonography of the stomach and duodenum, colonoscopy with multiple biopsies, 18F-FDG-PET, CT-scan of thorax and abdomen, ultrasound of lymph nodes, thyroid and salivary glands as well as a bone marrow biopsy showed restriction of the lymphoma to the stomach, corresponding to stage I disease. Thyroid ultrasound, however, was suggestive of chronic autoimmune thyroiditis, which was also verified by the presence of elevated thyroid autoantibodies with subclinical hypothyreosis (TSH 8.9 mU/L and thyreoglobulin-autoantibodies 424 ng/mL).

Consecutive serial gastroscopies performed every three mo showed no chance of the MALT lymphoma infiltrate 1.5 years after initial diagnosis and chemotherapy with the nucleoside analogue cladribine was initiated. Treatment consisted of 0.12 mg/kg cladribine given i.v. days 1-5 every 28 d for four courses, resulting in complete remission (CR) of the gastric MALT lymphoma.

Thirteen months after initial CR, a control gastroscopy disclosed histological evidence for *H. pylori*-negative, t(11;18)(q21;q21)-positive relapse of gastric MALT lymphoma and endosonography showed enlarged lymph nodes along the lesser curvature. Consequently, the patient received radiotherapy at a dose of 46 Gy and again achieved a histologically verified CR. Upon the third follow-up gastroscopy, however, the presence of probable minimal residual disease (pMRD) was suspected and the CR was rated as a probable sampling error. All gastroscopies until the patient's death repeatedly disclosed pMRD without progression in spite of the fact that no therapy was given.

In July 2004, the patient developed acute dyspnea and a CT scan showed a subglottic mass leading to massive tracheal compression. Histological assessment showed the presence of anaplastic large B-cell lymphoma associated with Epstein-Bar virus. Molecular assessment

disclosed the absence of t(11,18)(q21;q21) and no clonal relationship to the initial MALT lymphoma and was thus rated as a second malignancy. Two cycles of chemotherapy were administered containing rituximab, mitoxantrone, cyclophosphamide and vincristine, resulting in complete remission of the lymphoma. The patient, however, refused any further therapy and remained in CR until February 2006, when the patient had to be re-admitted due to rapidly progressing dyspnea and deteriorating general condition, resulting in the patient's death in May 2006.

In February 2008, the patient's daughter was admitted at our institution at the age of 55 years. After having been diagnosed with SS in 1993, she had developed a painless swelling in the right parotid gland. Ultrasound and a consecutive MRI were suggestive of a Warthin tumor and the patient underwent superficial parotidectomy. Upon histological assessment, infiltration of the parotid with MALT lymphoma was found. Apart from the diagnosis of SS with consecutive dryness of eyes and mouth, the patient's general condition was excellent and her medical history uneventful.

The lymphoma was analyzed for MALT lymphoma specific genetic aberrations including RT-PCR for t(11;18)(q21;q21) as well as FISH for t(14;18) involving IGH/MALT and assessment of trisomies 3 and 8, yielding negative results. For staging, a CT scan of thorax and abdomen and MRI of orbit, salivary glands and the cervical region were performed. Findings were inconspicuous except enlarged bilateral lymph nodes measuring up to 22 mm, which were rated as involvement with lymphoma. However, no histological verification of these lymph nodes was done. In view of the mother's medical history, a gastroscopy and a bone marrow biopsy were performed. No evidence of lymphoma involvement was seen on these investigations and the patient was rated negative for *H. pylori* both on histology as well as serology. As the patient was asymptomatic and without documented progression of the disease, she is currently on a wait-and-see strategy with radiological assessment consisting of MRI of salivary glands and cervical region as well as a CT of thorax and abdomen every 3 mo.

DISCUSSION

A familial background of non-Hodgkin lymphoma or other lymphoproliferative malignancies has repeatedly been reported as a significant risk factor for NHL. A computerized literature research identified nine recent analyses, including a total of 21 378 patients with NHL for assessment of familial risk[7,8,13-19]. An analysis of the Swedish Family Cancer Database, including 4.445 patients diagnosed with NHL having at least one first-degree relative diagnosed with NHL, has assessed the familial risk in terms of standardized incidence ratios (SIRs). A first-degree relative suffering from NHL significantly increased the general risk for NHL (SIR = 1.8), with the SIR for diffuse large B-cell lymphoma being 1.8, follicular lymphoma 2.0 and "B-cell lymphoma, not otherwise specified" being 3.4[8].

Wang *et al*[18] evaluated 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium comprising 17 case control studies and reported similar results. The overall NHL risk for a person with a first-degree relative compared to a stratified control collective was reported at an odds ratio (OR) of 1.5. Controversial findings, however, were reported whether a parent or sibling with NHL provides a higher risk for consecutive NHL-development. Furthermore, the level of risk seemed to be higher for histopathological specific concordant neoplasm than for other subtypes in various reports, but due to the limited number of cases, statistical significance was not reached[8,18].

While infectious agents and autoimmune diseases have repeatedly been linked with MALT lymphoma pathogenesis, no data on a familial background in patients with MALT lymphoma have been published so far.

As it is, the case of the patient with gastric MALT lymphoma also highlights various clinically relevant points. First of all, it underscores the potential influence of chronic autoimmune disease on the development of gastric MALT lymphoma, as recently highlighted by Troch *et al*[20]. As has been shown, these lymphomas might be independent of *H. pylori* even at early stages and the presence of an underlying autoimmune disease has been reported as a negative prognostic risk factor for lymphoma regression after *H. pylori* eradication[4]. In addition, the lymphoma cells in our patient harbored the t(11;18)(q21;q21) translocation, which is also thought to confer resistance to antibiotic therapy. Consequently, no response was seen with *H. pylori* eradication and chemotherapy subsequently resulted in complete remission (CR). This CR was nevertheless relatively short and consecutive radiation resulted in pMRD, which was initially erroneously assessed as CR probably due to a sampling error. In spite of the fact that no further therapy was applied, the MALT lymphoma was stable for a prolonged time, i.e., until the patient's death. This is in keeping with recent data published by Fischbach *et al*[21] who have shown that patients with pMRD after *H. pylori*-eradication should not undergo further therapy, as has also been underscored by the recently published EGILS-consensus for management of gastric MALT-lymphoma[22]. To our knowledge, the cases presented in this article constitute the first report of MALT lymphoma developing in first degree relatives. A computerized search of the published literature disclosed no information on MALT lymphoma and a familial background, and "MALT lymphoma" as a distinct lymphoma entity was not listed in the Swedish Family Cancer Database or in any other article related to familial NHL development.

The MALT lymphomas diagnoses in our patients, however, showed different characteristics, as the mother's lymphoma developed in the stomach, while the daughter was diagnosed with parotid MALT lymphoma. As expected in a t(11;18)(q21;q21) positive gastric MALT lymphoma, no response to *H. pylori* eradication was seen and necessitated chemotherapy. In the parotid MALT lymphoma, no

genetic abnormalities could be detected and no evidence of gastric MALT lymphoma or *H. pylori* infection was seen at a staging gastroscopy. Interestingly, both mother and daughter suffered not only from MALT lymphoma but were also diagnosed with an autoimmune disorder (chronic autoimmune thyroiditis in the mother, SS in the daughter).

To date, no familial background for the development of MALT lymphoma has been reported, but our cases nevertheless suggest that the combination of autoimmune disease and MALT lymphoma in a first degree relative might constitute a risk factor for consecutive MALT lymphoma development.

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Events Calendar 2012

January 14-17, 2012
10th Oncology Controversies and Advances Update
Steamboat Springs, CO, United States

January 19-21, 2012
EASL Monothematic Conference: IMLI - Immune Mediated Liver Injury
Birmingham, United Kingdom

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL, United States

February 2-4, 2012
2012 Genitourinary Cancers Symposium
San Francisco, CA, United States

February 6-8, 2012
Pediatric Cancer Translational Genomics
Phoenix, AZ, United States

February 8–10, 2012
The 84th Annual Meeting of Japanese Gastric Cancer Association
Osaka, Japan

February 10-11, 2012
Cancer Survivorship for Clinicians
Seattle, WA, United States

February 14-17, 2012
ASCO Multidisciplinary Cancer Management Course
Eldoret, Kenya

February 20-24, 2012
Word Conference on Colorectal Cancer
FL, United States

February 22-23, 2012
National Cancer Institute Annual Biospecimen Research Network Symposium: "Advancing Cancer Research Through Biospecimen Science"
Bethesda, MD, United States

February 22-25, 2012
30th German Cancer Congress
Berlin, Germany

February 24, 2012
ASCO-German Cancer Society Joint Symposium, German Cancer Congress
Berlin, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 7-8, 2012
First International Gulf Joint Conference: Management of colon, breast, and lung cancer (Joint Symposium)
Dammam, Saudi Arabia

March 9-10, 2012
ESMO Conference on Sarcoma and GIST
Milan, Italy

March 10-11, 2012
Colorectal Polyps and Cancers: A Multidisciplinary Approach
Scottsdale, AZ, United States

March 17-21, 2012
Methods in Cancer Research Workshop (Advanced Cancer Course)
Al Asha, Saudi Arabia

March 22-24, 2012
The 1st St.Gallen EORTC Gastrointestinal Cancer Conference
St.Gallen, Switzerland

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 18-20, 2012
The International Liver Congress 2012
Barcelona, Spain

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA, United States

April 20–21, 2012
OOTR 8th Annual Conference - Organisation for Oncology and Translational Research
Kyoto, Japan

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV, United States

June 27-30, 2012
ESMO 14th World Congress on Gastrointestinal Cancer 2012
International Convention Center Of Barcelona,
Barcelona, Italy

July 1–5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association
Paris, France

July 5-7, 2012
International Research Conference on Liver Cancer
Heidelberg, Germany

July 6-8, 2012
The 3rd Asia – Pacific Primary Liver Cancer Expert Meeting "A Bridge to a Consensus on HCC Management
Shanghai, China

September 1-4, 2012
OESO 11th World Conference
Como, Italy

September 14-16, 2012
ILCA 2012 - Sixth Annual Conference of the International Liver Cancer Association
Berlin, Germany

September 21-22, 2012
Research Symposium, Inflammation and Cancer
Houston, TX, United States

October 15 - 17 2012
13th World Congress of the International Society for Diseases of the Esophagus
Venice, Italy

December 5-8, 2012
22nd World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists
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Acknowledgments

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

Statistical expression

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