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A case report of wound site seeding following cholecystectomy for dysplastic gallbladder

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ABSTRACT

Wound site metastasis following cholecystectomy is an uncommon but well recognised complication following laparoscopic surgery for unsuspected gallbladder carcinoma. We describe a case of implantation of dysplastic cells with subsequent malignant transformation at the incision site 3 years post-cholecystectomy for an inflamed gallbladder. Histopathological examination of this tumour confirmed adenocarcinoma of pancreatobiliary origin, possibly secondary to gallbladder cells implantation and subsequent carcinomatous change.

Unlike previously reported cases, the present case has two unique features: Firstly, the histology of the resected gallbladder at the initial operation was that of a low-grade dysplasia and not carcinoma; and secondly, there was a long interval between initial surgery and subsequent development of the wound site tumour. This case highlights that careful handling of the specimen tissue intraoperatively is paramount as cells implanted in the wound site can survive and undergo malignant transformation. All new masses occurring along the surgical wound site should be followed up and investigated to exclude implanted tumours.

1. Case report

A 76 year-old Chinese female with a history of hypertension and hyperlipidemia first presented to the emergency department in May 2011 with fever of 1 day duration associated with a background of 2 months of persistent right hypochondrial pain. Physical examination revealed right hypochondrial tenderness with no palpable mass. Blood investigations showed an elevated white cell count (12.15×10^9/L), mild hyperbilirubinemia (bilirubin 39 umol), elevated transaminases (aspartate transaminase 105, alanine transaminase 96 and an elevated alkaline phosphatase (339 U/L). A CT scan of the abdomen showed intrahepatic and common ductal dilatation, with a focal calculus lodged in the gallbladder neck with distension and diffuse mural thickening of the gallbladder. There was no intraluminal calculus noted in the CBD. She was treated with intravenous ceftriaxone and metronidazole for acute cholecystitis. A subsequent magnetic resonance cholangiopancreaticogram (MRCP) was performed when repeat liver function tests showed a persistently elevated ALP of 271 U/L despite normalisation of bilirubin levels and transaminases. The MRCP confirmed acute cholecystitis with Type 1 Mirizzi's syndrome with resultant dilatation of the intrahepatic ducts. Her symptoms and liver function tests improved with antibiotic therapy and she was discharged well after 9 days and planned for an interval cholecystectomy (Figs. 1–5).

She underwent laparoscopic converted to open cholecystectomy in July 2011 by an experienced consultant surgeon. Intraoperative findings were that of Type 1 Mirizzi's syndrome with a stone lodged in Hartmann's pouch and compressing the common hepatic duct. The gallbladder was distended with thick mucus with a thickened and fibrotic wall. Dense fibrosis at Calot's triangle with difficulty in dissection prompted the decision for conversion to open surgery. A fundus-first cholecystectomy was performed and the impacted gallstone was retrieved via an incision made in the Hartmann's pouch and the cystic duct stump was then closed with PDS 4/0 sutures. Her immediate post-operative recovery was uneventful and final histology of the gallbladder showed chronic cholecystitis with areas of low-grade biliary dysplasia, clear of cystic duct margin and no evidence of invasive carcinoma. Her subsequent recovery was uncomplicated (Fig. 6).

In July 2014, she presented with a two month history of an enlarging painless epigastric mass. Examination revealed a firm and fairly well- circumscribed 4 cm nodule located at the medial aspect of the Kocher's scar. CT scan of the abdomen showed a 3.9×3.3 cm subcutaneous solid-cystic nodule directly abutting the linea alba and left rectus sheath with no extension into the muscle or peritoneum. There were no intra-abdominal masses,

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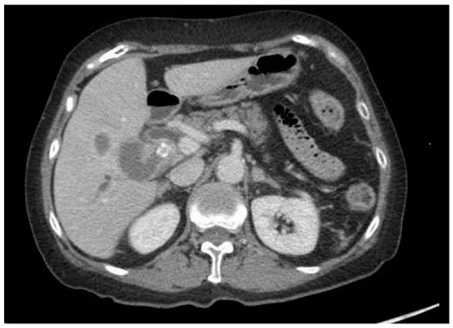

FIG.1

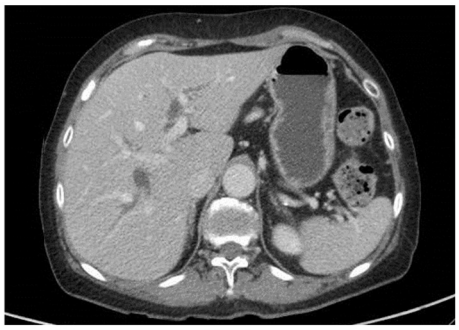

FIG.2

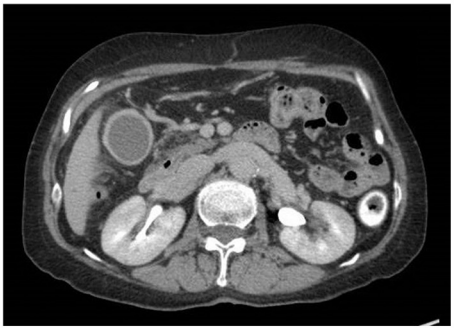

FIG.3

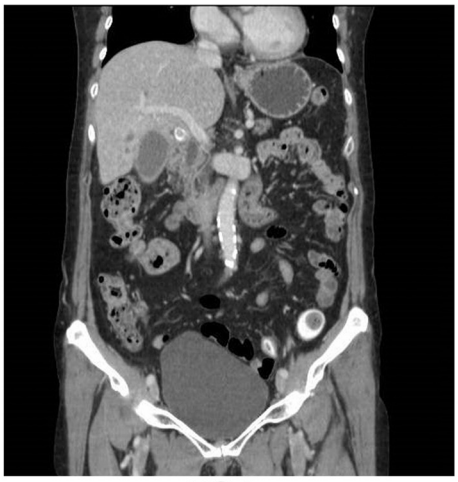

FIG.4

Figs. 1–4. CT images showing the presence of an impacted biliary calculus in the gallbladder neck with associated intra and extrahepatic biliary duct dilatation. There is also gallbladder wall thickening and pericholecystic fat stranding indicative of acute cholecystitis.

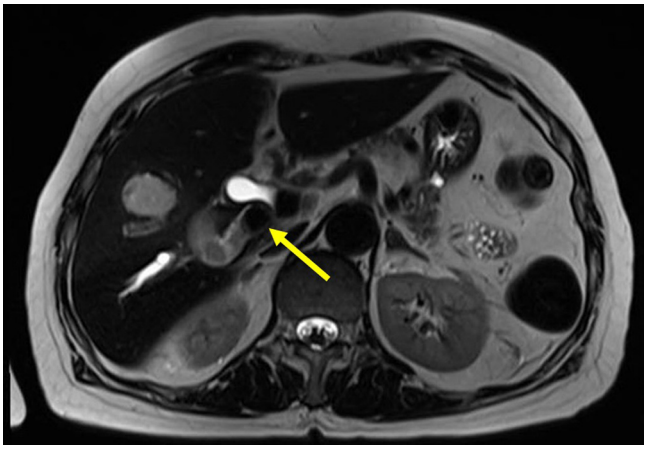

Fig. 5. MRCP image showing Type 1 Mirizzi's syndrome - yellow arrow showing the stone compressing the CBD causing upstream dilatation.

lymphadenopathy, peritoneal nodules or ascites. In view of the above findings, she was scheduled for an excision biopsy of the mass. However, as her pre-operative chest x-ray raised a suspicion of a left retrocardiac opacity, a CT thorax was performed. It confirmed no retrocardiac pathology and no suspicious lung lesions were seen. It also showed rather rapid enlargement of the epigastric nodule to 4.5 × 3.8 cm over 2 months, suspicious for a malignancy. A core biopsy of the epigastric mass showed atypical glandular proliferation with extracellular mucin and necroinflammatory exudate, suspicious for a mucinous neoplasm. Her Carcinoembryonic Antigen (CEA) and CA 19-9 were normal (2.8 and 5.4 UG/L respectively). She underwent wide excision biopsy of the mass in September 2014 and intraoperative findings were that of an 8 × 5 cm epigastric mass with a cystic appearance and greenish hue, adherent to the anterior sheath and linea alba. A transverse elliptical incision was made and a wide excision of the mass in its entirety was performed ensuring resection margins of at least 1 cm all around. There was no breach in the mass during resection. The subsequent 3 cm defect in the abdominal wall fascia following the excision was repaired with an Optilene® mesh. Histology of the epigastric nodule showed features

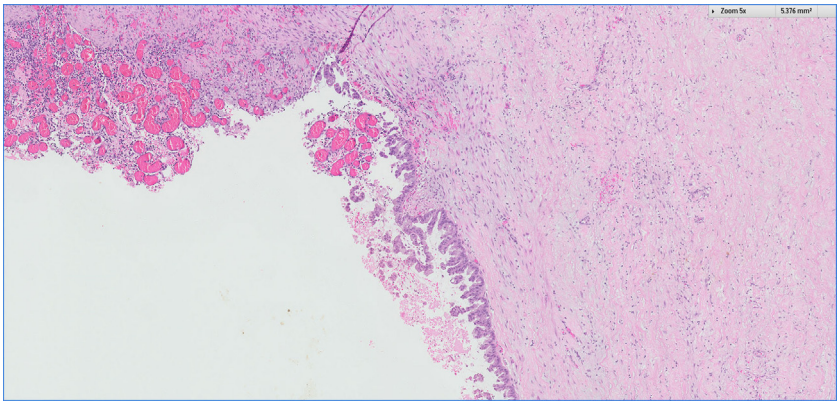

Fig. 6. Histology slide from the gallbladder showing areas of dysplastic biliary epithelium but no invasion is noted.

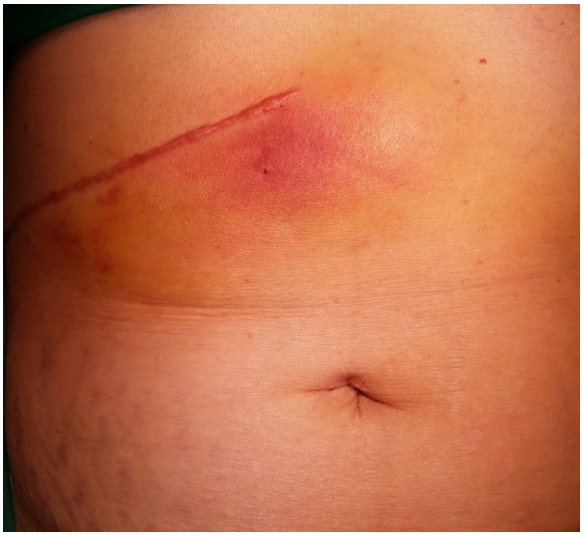

Fig. 7. Epigastric mass at medial aspect of Kocher's incision, and evident bruising from Tru-cut core biopsy.

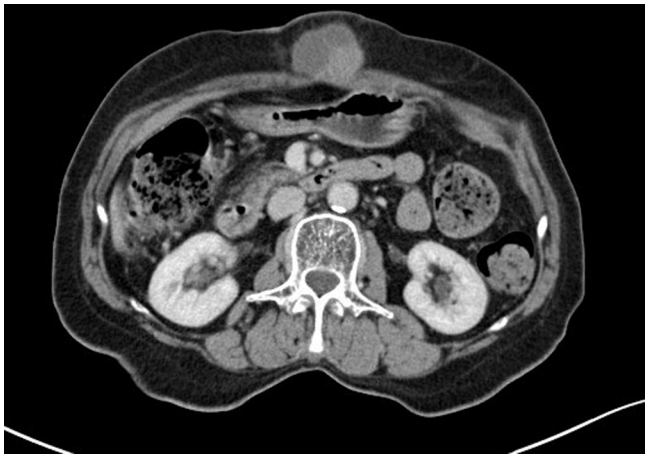

Fig. 8. CT scan of the abdomen showing the 3.9 x 3.3 cm subcutaneous solid-cystic nodule directly abutting the linea alba and left rectus sheath with no extension into the peritoneum.

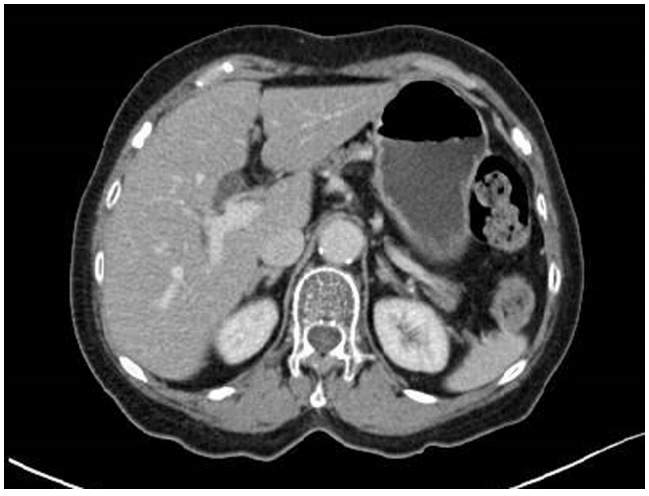

Fig. 9. Contrast-enhanced CT scan of the abdomen showing no tumour recurrence at the gallbladder resection bed or liver and absence of lymphadenopathy.

of an adenocarcinoma with a papillary architecture and a surrounding fibrous capsule. Cystic space containing blood and mucin was noted, with no obvious lymphovascular invasion seen. On immunohistochemical staining, the tumour cells showed positivity for CK7, SMAD4 and MUC 5AC and appeared negative for CK20 and TTF-1; features in keeping with adenocarcinoma from a pancreatobiliary origin, possibly secondary to tumour implantation or metastasis. Excision margins were clear of tumour (Figs. 7–13).

The patient was offered further investigations with PET/CT after discussion at a multidisciplinary tumour board meeting but she declined. We confirmed through phone correspondence that she has remained well and asymptomatic 30 months after her surgery.

2. Discussion

Wound or port site metastasis is an uncommon but recognised complication in patients undergoing laparoscopic surgery when malignancy is either proven or unsuspected. Port site metastasis was first described in 1978 by Dobronte et al. [1] in a patient who developed local tumour metastases in the abdominal wall two weeks after laparoscopic surgery for ovarian cancer was performed. It was attributed to the infiltration of malignant ascites into the port sites during trocar insertion. Since then, there have been numerous reports of wound or port site metastasis in patients with gastrointestinal, urological and gynaecological malignancies (such as colorectal, ovarian) in the literature. Paolucci et al. [2] reported that 17.1% (70 out of 409) of patients undergoing laparoscopic cholecystectomy for non-diagnosed gallbladder carcinomas subsequently developed port- site recurrence. These patients were incidentally found to have gallbladder carcinoma on histology fol-

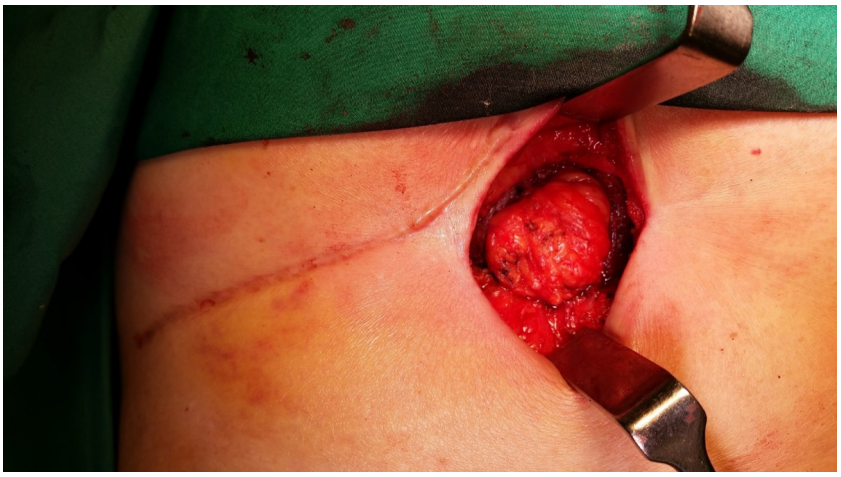

Fig. 10. Intraoperative findings of an 8 x 5cm epigastric mass adherent to the anterior sheath and linea alba.

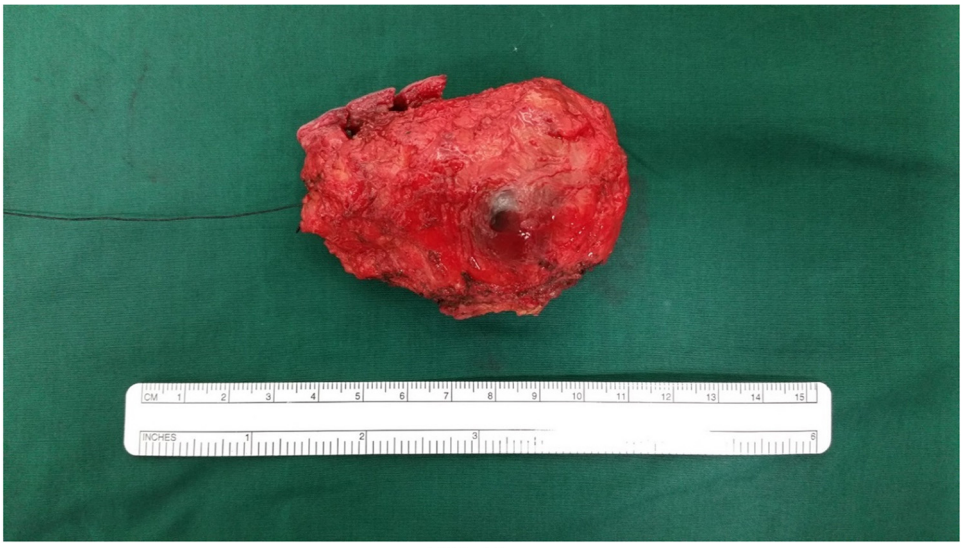

FIG.11

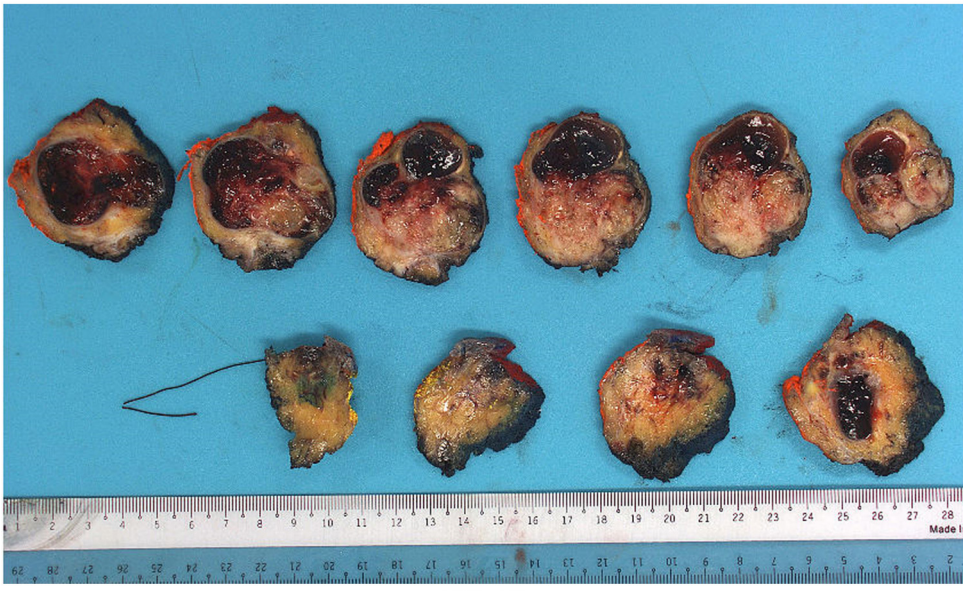

FIG.12

Figs. 11 and 12. Resected epigastric solid-cystic mass containing mucoid material upon sectioning.

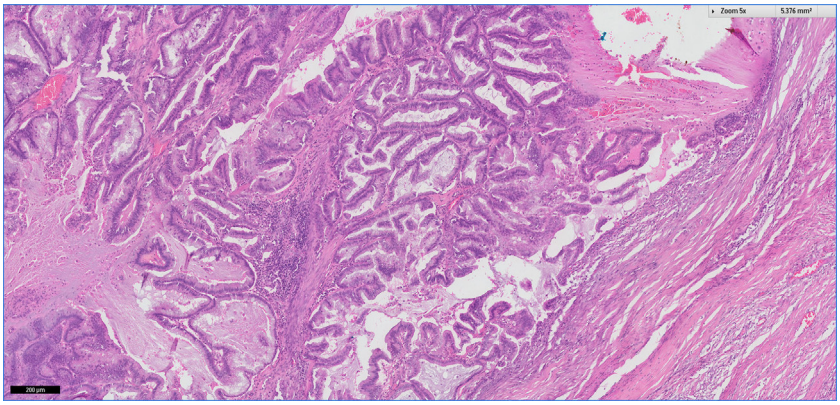

Fig. 13. Histology slide of the epigastric mass showing features of an adenocarcinoma with a papillary architecture. Cystic space containing blood and mucin noted.

lowing routine cholecystectomy for gallstone disease. We aim to focus our discussion on patients developing wound site metastasis following cholecystectomy (laparoscopic or open) for gallbladder carcinoma. The incidence of port site metastasis from gallbladder carcinoma range from 10 to 17% in the literature [2–6], with the median time for recurrence at the port site following cholecystectomy being 7 months [2]. There are relatively more reports of port site recurrence in the literature and it is recognised as a form of loco-regional recurrence of the carcinoma.

The development of gallbladder cancer is proposed to occur over a span of 5–15 years, with the presence of stepwise tissue alterations such as metaplasia, dysplasia, carcinoma in situ, and finally invasive cancer [7]. Two distinct pathogenesis pathways leading to gallbladder cancer have been hypothesized: (1) a dysplasia-carcinoma sequence arising from metaplastic epithelium and (2) an adenoma-carcinoma sequence. [8,9] For the purpose of this report, we will focus on the first pathway – the dysplasia-carcinoma sequence. This sequence is considered to be the more important model of carcinogenesis than the adenoma-carcinoma sequence, as less than 3% of early carcinomas have adenomatous remnants, suggesting its limited importance in the carcinogenic pathway. In this sequence, chronic inflammation of the gallbladder can result in metaplasia which occurs in two forms: gastric and intestinal type; similar to metaplasia of the stomach. This then leads to dysplasia (following further inflammation) which then progresses to carcinoma in situ (CIS), which subsequently becomes invasive. This theory is supported by the finding that over 80% of invasive gallbladder cancers have adjacent regions of CIS and epithelial dysplasia [10]. Gallbladder dysplasia typically progresses to invasive cancer over a latency period of 15–19 years [11]. A study by Solaini et al. [11] found that incidental gallbladder dysplasia was higher in Asian patients (3.5% vs.1.2%, $p = 0.02$), and in the context of a negative cystic duct margin, gallbladder dysplasia can be considered fully treated following cholecystectomy.

To our knowledge, there have been no previous cases in the literature on wound site implanted dysplastic tissue transforming to carcinoma; and this may be the first such report of dysplastic cells remaining viable in an ectopic site and subsequently proliferating to form a malignant growth. Our case has been reported in line with the SCARE criteria [12], a 14-item checklist that was formulated to help improve the reporting quality of case reports.

Unique to this case is the initial histology of the resected gallbladder which was that of low grade dysplasia with no evidence of invasive carcinoma, and the cystic duct margins were clear of dysplasia. Furthermore, the CT scan performed three years after the initial surgery did not show any recurrence at the gallbladder resection bed, liver or elsewhere in the abdomen; and there was no lymphadenopathy as well. We postulate that in this patient, there may have been direct seeding of the wound (from potential bile spillage during extraction of the stone in Hartmann's pouch) with subsequent malignant transformation of the dysplastic cells. This is supported by the fact that the interval between the initial cholecystectomy and development of the tumour was three years, much longer than the median time of 7 months reported for cases of gallbladder carcinoma. It is regrettable that the patient declined further investigations which would have enabled us to ascertain with certainty that this was the case.

Possible factors for wound or port site metastasis include direct seeding of wound by spilled bile or tumour cells, haematogenous dissemination of tumour cells or pneumoperitoneum-induced shedding of tumour cells into the peritoneal cavity. During surgery, the ongoing passage of instruments in and out of the port sites following dissection can potentially result in direct seeding of the port sites with tumour cells. Tissue trauma during port insertion also results in a hyperaemic state which provides an excellent environment for circulating tumour cells to implant in sites with increased blood supply. Furthermore, insufflation of carbon dioxide results in distension of abdomen with resultant high intraperitoneal pressure causing shedding of tumour cells into the peritoneal cavity [13]. Pneumoperitoneum also results in peeling of the muscular layer of the abdominal peritoneum which increases the likelihood of tumour cell adhesion at port sites with subsequent healing resulting in scarring and entrapment of tumour cells [14]. An in-vitro study by Aoki et al. [15] to determine the effect of peritoneal injury on tumour implantation showed that mice (with intraperitoneal injection of cultured human gallbladder cancer cells) who were subjected to laparoscopic trocar insertion and peritoneal perforation had significantly higher implantation rate than controls (90–100% vs 0%, $p < 0.01$).

Perhaps the most important factor for development of wound site metastases is surgical technique. In laparoscopic surgery, there is potential for traumatic handling of the gallbladder with higher risk of perforating the gallbladder and subsequent spillage of bile and dissemination of tumour cells [16]. The subsequent implantation of tumour cells in the port or wound sites is further aided by the processes described above.

However, with laparoscopic surgery being rather ubiquitous in this day and age, port site metastasis can be reduced by ensuring meticulous surgical resection, careful handling of the tumour to avoid spillage of cells or bile, rinsing of wound and instruments and use of protective measures such as wound protectors or specimen retrieval bags during extraction of tumour. In skilled and careful hands, the risk of seeding of malignant cells during laparoscopic cholecystectomy may potentially be less than open surgery.

Wound or port site metastasis is a strong risk factor for peritoneal dissemination of disease (via mechanisms explained above)

and a proper diagnostic workup should include imaging such as FDG-PET/CT to look for distant and peritoneal metastases. FDG-PET is increasingly used to identify and stage various tumours. Most malignant tumours show increased uptake of FDG because malignant transformation and growth of tumour cells is associated with overexpression of glucose transporters and increased hexokinase activity [17]. There have been studies showing the utility of FDG-PET in diagnosis of gallbladder cancer. Koh et al. [18] found that FDG-PET identified gallbladder carcinoma with 81.3% accuracy, 75% sensitivity, and 87.5% specificity. A study by Antonio et al. [19] had similar results, with a sensitivity of 80% and specificity of 82% in diagnosing gallbladder cancer. The combination of FDG-PET/CT has the added benefit of providing structural and functional information to increase sensitivity and specificity in the diagnosis and staging in gallbladder carcinoma, especially in those with atypical presentations or port site metastases. It can rule out any other primary tumour as the source of metastasis, and this is especially important when the initial histology is negative for malignancy and when there is a late presentation. In the absence of distant metastases, treatment should involve wide excision of the port site and exploration of peritoneal cavity via either a laparotomy or diagnostic laparoscopy to exclude peritoneal metastasis. In this case, a wide excision of the epigastric mass was performed as empirical treatment initially as the mass was noted to be rapidly enlarging and the true nature of the mass was not apparent during the initial core biopsy. We feel that wide excision in the absence of distant metastases offers a chance at adequate local control, which in turn decreases the risk of recurrence. We appreciate the lack of evidence to guide treatment of such rare cases.

3. Conclusion

Wound or port site metastasis is a fairly uncommon complication of laparoscopic oncologic surgery. Although various factors have been implicated as contributing factors, meticulous surgical technique remains the most important factor in preventing this. Furthermore, this case highlights that careful handling of tissue specimens intraoperatively is paramount as implantation of pre-malignant tissue can lead to progression and subsequent development of carcinoma in the incision or port site. All new masses occurring along a surgical wound site should be followed up and investigated to exclude implanted tumours. We recommend investigating such patients with a PET/CT scan and complete surgical excision of such tumours should be the mainstay of treatment.

Conflicts of interest

The authors declare no conflicts of interest.

Sources of funding

No funding or study sponsors were required for this study.

Ethical approval

No ethics committee approval was required.

Consent

We have obtained written consent from the single patient mentioned in this case report.

Authors contribution

Annalisa Ya-Lyn Ng (Corresponding Author) – Data collection, Literature search and Manuscript drafting.

Qing Ting Tan – Surgeon involved in care of patient, Data collection, Literature search and Manuscript drafting.

Wan Wei Keat – Pathologist involved in reading the histology and providing the histological slides.

Yaw Chong Goh – Primary Surgeon involved in care of patient, Editing of manuscript and overall review.

Registration of research studies

Researchregistry1673.

Guarantor

Annalisa Ya-Lyn Ng.
Qing Ting Tan.
Yaw Chong Goh.

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