Port-Site Metastasis: Tip of the Iceberg?

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In 1870 Reincke[1] reported two cases in which tumors developed at the sites of paracentesis for ascites due to peritoneal carcinomatosis. History was repeated in a different context when two cases of port-site metastasis[2] were reported in 1993. In the last 200 years tumor spread has remained a difficult phenomenon to understand, and minimal access surgery has added several more questions.

Port-site metastasis has gained the attention of not only minimally invasive surgeons but also the media. Performing an operation for a benign condition is quite different from performing one for a malignant condition. Patients suffering from the latter may not value the advantages of minimal access surgery if there is an increased risk of tumor spread and less of a likelihood for cure.

The phenomenon of port-site metastases should be studied in conjunction with tumor biology. Therefore, we have briefly reviewed the principles of tumor spread pertinent to the understanding of this subject. We have followed this with a brief account of three cases of port-site metastasis and two cases of cutaneous metastasis following conventional surgery for comparison. Some of these cases had been operated on by other surgeons in the past but were seen and operated by our group during their follow-up.

GENERAL ASPECTS OF TUMOR SPREAD

Metastasis is defined as the transfer of disease from one organ or part thereof to another not directly connected with it.[3] This is due to the transfer of malignant cells which is one of the main problems in oncological surgery. There are five main steps involved in the tumor spread:

1. Infiltration of surrounding tissue and penetration of lymphatics and blood vessels.
2. Release of single cells or groups of malignant cells to the circulation.

3. Survival of malignant cells in the circulation.
4. Arrest of malignant cells in the capillary beds of distant organs.
5. Penetration of vasculature and or lymphatics followed by growth of malignant cells.

The pathogenesis of tumor invasion is not very well understood. It may occur as a result of the following:
1. Mechanical pressure.
2. Release of lytic enzymes.
3. Increased motility of malignant cells. Cinematography has shown that tumor cells are capable of active movement and migration. Autocrine motility factor can stimulate the motility of cells.

Transcelomic spread is a well-recognized means of tumor spread.[4] When a tumor invades the serosal layer of a viscus, it excites an inflammatory response which leads to effusion. Malignant cells can become entangled with the fibrinous exudate; they can also become detached and be swept away into the peritoneal cavity by serous fluid. They settle widely on its wall, proliferate, and give rise to innumerable seedlings. The most common example of transcelomic spread is seen in the peritoneal cavity in cases of primary gastric, colonic, and ovarian carcinomata. The greater omentum can become heavily infiltrated. Metastases are common in the pouch of Douglas due to a gravitational effect. Transpleural spread occurs in some cases of lung and breast cancer.

METASTASIS BY IMPLANTATION ON EPITHELIAL SURFACES

Another method of spread is inoculation metastasis by implantation of detached tumor cells on epithelial surfaces.[5] There are reported cases of the spread of carcinoma from one lip to the other, from one vocal cord to the other, or from one side of the vulva to the other. Secondary growths in the hollow epithelial viscera at a distance from the primary growth have been attributed to surface implantation of tumor fragments transported within cavities of viscera (e.g., from one lung to the other, from one part of the alimentary tract to another intraluminally, from the gallbladder to the intestine, from ovary to uterus via the Fallopian tube, or from the renal pelvis and ureter to the bladder).

Inoculation metastasis can occur but is not common, as there are several physiological factors which prevent it from happening. The presence of a rich bacterial flora on the skin, the diminished viability of fragments of tumor, and the absence of breaches in healthy epithelial surfaces make inoculation metastasis uncommon. Before concluding that a metastasis is purely from inoculation, it is very important to exclude multiple primary growths and metastases by other routes such as trancelomic, lymphatic, and bloodborne. Multifocal tumor formation is responsible for most cases of contact cancer.

DORMANT TUMORS

Metastases may appear several years after a primary tumor has been resected. This feature of dormancy is most often seen in carcinoma of the breast and malignant melanoma.[4] The patient may develop metastases 35 years after excision of the primary tumor. The patient usually remains well during the dormant period. There may be no local recurrence. The appearance of metastases may have no precipitating factor. However, it may follow a severe illness, an operation, or psychological stress. The disease may progress rapidly once the metastases have appeared. The natural history of most cancers in relation to tumor spread is still poorly understood.

SURGICAL TRANSPLANTATION AND INOCULATION OF TUMORS

Intentional transplantation of tumors in human beings is a cruel experiment which should never be performed. Nevertheless, such experiments were conducted by some surgeons in the 19th century.[5] Skin tumor nodules were transplanted into normal skin. One case was reported where a breast tumor from one breast was transplanted into the normal breast. These experiments show that it is feasible surgically to transplant tumors into a normal area.

Metastases caused by surgical innoculation at incision sites have been reported over many years. Mayo[6] reported recurrent tumors at suture sites following gastrectomy for carcinoma of the stomach. Kettle[7] reported a metastasis at the puncture site of needle aspiration of a suspected liver abscess. German[8] viewed metastasis from endometrial tumors at the operative site as secondary to the implantation of cells. However, Nicholson[9] believed it to be due to metaplastic change in celomic tissue.

There has been a considerable controversy about the presence of malignant cells in the peritoneum following operations for oncological conditions. Moore et al.[10] reported that the peritoneal lavage fluid following operations for malignant conditions of the stomach, colon, rectum, ovary, uterus, and cervix contained malignant cells. If the colorectal tumors were inoperable, 95% of the cases contained malignant cells in comparison with 17.5% in operable cases. Juhl et al.[11] used immunocytochemical techniques and showed 39% of patients operated for carcinoma of the stomach, colon, rectum, and pancreas contained intraperitoneal malignant cells. They also showed a direct correlation between the stage of cancer and the presence of intraperitoneal malignant cells. It is not clear whether these cells play a role in implantation metastasis, as wound recurrence is not as high as these quoted figures.

There has been much debate about the viability of disseminated neoplastic cells especially in the lumen of the large intestine. Rosenberg et al.[12] doubted that this could be the case for exfoliated cells found in the lumen of the bowel in the case of colorectal cancer. However, Umpelby and colleagues[13] reported that exfoliated cells in the intestinal lumen recovered in the same conditions had an overall viability rate of 90% irrespective of the size of the tumor (Duke's staging or histological grading). They also showed that cells can grow in a culture medium for as long as 10 days and, if injected into the tail vein of immunodepressed mice, can cause pulmonary tumors. Tanida and coworkers[14] showed that neoplastic cells disseminated in the peritoneum from gastric cancers can remain viable. This has been reconfirmed by Isuka et al.[15] using the technique of H3 Thymadine incorporation.

CASE REPORTS

Five illustrative cases of metastasis following surgery are presented.

Case 1

A 52-year-old woman was extensively investigated by her gastroenterologists and gynecologists for abdominal pain of

more than two years. The only positive finding was the presence of gall stones, to which only some symptoms could be attributed. She underwent an elective laparoscopic cholecystectomy using the four-port technique. During laparoscopy, no associated pathology was discovered. A redivac drain was inserted in the right lateral port which was removed 24 hours postoperatively. She was sent home the following day and symptomatically improved. She was reviewed six weeks after the operation and was discharged from the clinic. Twelve months after the operation, she presented with pain at the right midclavicular port site. On examination, a stitch granuloma was suspected. The growth, with stitch, was excised and identified histologically as an adenocarcinoma. The primary source could not be conclusively determined; thus the patient underwent further extensive investigations. A CT scan of her abdomen suggested an ovarian primary source. We performed a diagnostic laparoscopy which confirmed advanced ovarian tumor with extensive intra-abdominal metastases.

Case 2

A 72-year-old male presented with hematemesis. Endoscopy revealed ulceration on the posterior wall of the stomach. Biopsies revealed stromal cell tumor of the stomach, and the patient underwent laparoscopic partial gastrectomy.[16] The tumor was removed through the port in the left hypochondrium, but the retrieval bag burst in the process. Four months postoperatively he presented with a nodule at the infraumbilical port site. The nodule was excised, sent for histological study, and was identified as a metastatic deposit of stromal cell tumor. CT scan of the patient's abdomen confirmed extensive intra-abdominal metastases, and he later developed a metastasis in the extracted port site as well.

Case 3

A 56-year-old male underwent laparoscopic anterior resection. In his follow-up examination, his serum CEA was found to be rising. Twelve months postoperatively, a recurrence at the anastamotic site and clinically palpable lumps in the abdominal wall were found. CT scan and second laparotomy confirmed extensive intra-abdominal metastases in addition to metastases in the abdominal wall.

Case 4

A 71-year-old female underwent conventional anterior resection for carcinoma of the rectum. Eight years later she was found to have a recurrence at the site of anastamosis and underwent another resection by conventional technique. Hemorrhage occurred during the second operation and a drain was inserted. Two years later she presented with a metastastic nodule between the main incision scar and the drain site in the left iliac fossa. The nodule was excised under general anesthesia.

Case 5

An 88-year-old male presented with peritonitis. A CT scan performed showed collection in the left paracolic gutter, which was determined to be an abscess upon aspiration. He underwent conventional left hemicolectomy and resection of the adherent small bowel for a perforated Duke's C1 adenocarcinoma of the colon. Six months after the initial operation, he presented with a metastasis at the aspiration site, which was excised. Nine months after the operation, he presented with a metastatic deposit at the site of main incision which was also excised. Despite all these recurrences, the patient remained clinically well for his age and condition when he was seen nine months after the last operation.

PORT-SITE METASTASIS

Port-site metastases may represent only the beginning of such findings, as patients may also have extensive metastases within the abdomen.

The simplest explanation of the problem is that malignant cells could be transferred to the trocar wound site during the operation and give rise to port-site metastases. However, the real problem may be more complex. In case 1, the patient had a redivac drain in the right lateral port for 24 hours but developed a port-site metastasis at the site of the midclavicular port. In case 2, the tumor was removed through the left lateral port, but the metastasis was seen initially in the umbilical port site which was used only for the telescope. In case 3, one of the metastases in the abdominal wall was some distance from the port site. The site of metastasis in relation to the port appears to be unpredictable in these cases, and an evaluation is needed to determine whether there is any relationship between the use of a particular port and metastasis.

In cases 1 to 3, it is difficult to conclude that the port-site metastasis was purely an inoculation metastasis introduced via the port, as the patients had extensive metastases in the abdomen. The trancelomic and lymphatic routes cannot be excluded. It remains to be seen how many of such cases reported in the future will be purely inoculation metastasis at the port site or part of a widespread disease. In case 1, the histology of the gallbladder was normal. Other investigators[17] have reported port-site metastasis after removing gallbladders with histological evidence of adenocarcinoma. It is not clear whether port-site metastasis is dependent on the quantity of tumor cells implanted at the site of the port. It may be dependent on both "seed and soil."

Difficulties in surgical dissection and tumor removal may play a role in cutaneous metastasis. However, in case 1 no dissection was performed near the undetected tumor in the patient's ovary. In case 2, the tumor was removed through the left lateral port, although the metastasis was initially seen near the umbilicus. In case 3, there was a metastasis some distance from the port site. Therefore, one cannot presume that difficulties in dissection and tumor removal are the sole contributors to port-site metastasis. Furthermore, the effect of increased intra-abdominal pressure on malignant cell dispersion within the abdomen, cell motility, and cell permeation are not known, and this warrants considerable research in the future.

The duration of the interval between the original operation and cutaneous metastasis is variable (case 1: 12 months; case 2: 4 months; case 3: 12 months; case 4: 8 years after the first operation, 4 years after the second operation; case 5: 6 months for the first metastasis, 9 months for the second metastasis). Cava and colleagues[18] reported a subcutaneous metastasis seven days after laparoscopy in a patient with adenocarcinoma of the stomach. Malignant cells can remain dormant in patients presenting with metastasis after a considerable period of time. This warrants long-term follow-up of patients to evaluate what percentage of patients develop port-site metastases.

Drains are known to predispose the patient to metastases. Malignant cells contained in the peritoneal fluid may provide a greater dose of inoculation

over a longer period at the drain site. It is not clear whether malignant cells survive longer in wounds of smaller diameter, which would be relevant to port sites, nor is it known whether the smooth surface of the ports has any effect on cell survival. Preventive factors, such as washing the port site with locally acting chemotherapeutic agents, need to be evaluated.

CONCLUSION

For many years, it has been recognized that local factors are important in determining the sites of metastasis.[19] Murthy et al.[20] have shown experimentally that the frequency of tumor implantation is greater when cancer cells are presented to wounds in their early, rather than in their late, stages of healing. Tumor cells reaching the operative sites bind to fibrin and become entrapped in the fibrin gel. These newly implanted cells may benefit from the surgically induced depression of host immunity and the release of growth factors from the regenerating tissues. These factors may play a role in the port-site metastasis. It would be more worrisome if minimal access surgery led to widespread metastasis for whatever reasons and port-site metastasis were only the tip of the iceberg. Whether the frequency of metastasis is higher after minimal access surgery in comparison with conventional surgery has also not yet been determined. Randomized clinical studies are still awaited.

In this report and in our previous work on the subject, we have used the term "port-site metastasis."[2] However, "metastases following minimal access surgery" may be a more appropriate term, as it gives a broader view of the subject. The discussion thus far and in cases reported raises a number of questions. Extensive research in this area is needed, as a number of questions pertaining to the mechanism of these recurrences still must be answered.

It is hoped that clinicians and basic scientists will contribute to the understanding of "metastases following minimal access surgery," which are detrimental to the practice and survival of laparoscopic oncological surgery. STI

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