Cutaneous metastases secondary to pancreatic cancer

Kei Horino, Hiroshi Takamori, Yoshiaki Ikuta, Osamu Nakahara, Akira Chikamoto, Takatoshi Ishiko, Toru Beppu, Hideo Baba

INTRODUCTION

Secondary neoplasm involvement of the skin seems to be rare from an anatomical point of view. It is reported that the incidence of cutaneous metastases secondary to pancreatic cancer is 2.0% of all metastases but sometimes it appears as a first symptom of advanced pancreatic cancer. Several cases of this condition have been reported, especially as umbilical metastases, that is, a Sister Mary Joseph’s nodule (SMJN). The most common metastatic tumors of the skin are derived from breast, lung, stomach, colon, head and neck, renal cancers and melanoma. We evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

MATERIALS AND METHODS

We treated two patients and found 64 patients with cutaneous metastases from pancreatic cancer in the literature. The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients who were treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment. Prognoses of cutaneous metastases are similar to other metastatic sites from pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

CONCLUSION: The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancers. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

© 2012 Baishideng. All rights reserved.

Key words: Cutaneous; Metastasis; Pancreas; Cancer; Prognosis

Peer reviewer: Intiaz Ahmed Wani, MD, Amira Kadal, Srinagar, Kashmir 190009, India

Horino K, Takamori H, Ikuta Y, Nakahara O, Chikamoto A, Ishiko T, Beppu T, Baba H. Cutaneous metastases secondary to pancreatic cancer. World J Gastrointest Oncol 2012; 4(7): 176-180 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/176.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.176

Abstract

AIM: To evaluate prognoses after cutaneous metastases, derived from pancreatic cancer.

METHODS: We treated two patients with cutaneous metastases from pancreatic cancer. We reviewed 40 reported patients in addition to our cases and analyzed clinical features of cutaneous metastases from pancreatic cancer.

RESULTS: The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients who were treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment. Prognoses of cutaneous metastases are similar to other metastatic sites from pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.
We evaluated clinical parameters, including age, gender, symptoms, cutaneous metastatic site, primary site of pancreatic cancer and the receiving of chemotherapy or chemoradiotherapy (CRT). Survival curves were depicted using the Kaplan-Meier method and levels of significance were tested with the log rank test. Probability values < 0.05 were considered significant. Prognostic factors were assessed by odds ratios with 95% confidence interval using univariate and comparative analysis. Cox's proportional hazard model was used in a stepwise multivariate analysis for all parameters to identify factors independently associated with the prognosis.

### RESULTS

All 42 patients were diagnosed as pancreatic cancer due to histological examination from cutaneous and/or primary biopsy sample or imaging, including enhanced computed tomography or magnetic resonance imaging. The patient population comprised of 22 men and 20 women with a median age of 68 years, ranging from 36 to 85 years. Survival time ranged from 1 to 32 mo. The literature searched using PubMed and Igaku Chuo Zassi (in Japanese) from 1950 to 2011. Of 66 patients, 42 were analyzed to clarify clinical features because these patients were recorded in detail (Table 1).

| Age (yr) | Sex | Symptom | Appearance | Skin site | Primary | Prognosis | Other metastasis | Other therapy | Author |
|----------|-----|---------|------------|-----------|---------|-----------|-----------------|--------------|--------|
| 76       | F   | Present | Nodule     | Umbilicus | Tail    | 8 mo, dead | Peritoneum      | 5-FU, OK432   | Hisamoto et al[9] |
| 67       | F   | Absent  | Nodule     | Abdomen   | Tail    | 4 wk, dead | Liver           | No therapy    | Taniguchi et al[3] |
| 69       | M   | Present | Nodule     | Face, head | Head    | 5 mo, dead | Liver, lung, LN | No therapy    | Taniguchi et al[3] |
| 70       | M   | Present | Nodule     | Umbilicus | Tail    | 8 mo, dead | Peritoneum      | 5-FU, GEM, CRT | Taguma et al[16] |
| 67       | M   | Present | Nodule     | Inflammatory Chest, abdomen | Not detail | 5 mo, dead | Lung           | No therapy    | Taniguchi et al[3] |
| 55       | M   | Present | Nodule     | Umbilicus | Tail    | 2 mo, dead | Liver           | No therapy    | Ozaki et al[8] |
| 53       | M   | Present | Nodule     | Umbilicus | Tail    | 5 mo, dead | Peritoneum      | No therapy    | Miyahara et al[8] |
| 76       | F   | Present | Nodule     | Umbilicus | Tail    | 7 mo, dead | Peritoneum      | No therapy    | Miyahara et al[8] |
| 72       | M   | Absent  | Nodule     | Umbilicus | Tail    | 14 wk, dead | Liver, intestine | No therapy    | Miyahara et al[8] |
| 61       | M   | Present | Nodule     | Umbilicus | Body    | 4 wk, dead | Peritoneum      | No therapy    | Miyahara et al[8] |
| 67       | M   | Absent  | Nodule     | Umbilicus | Body    | 2 mo, dead | Peritoneum      | No therapy    | Miyahara et al[8] |
| 73       | F   | Absent  | Nodule     | Abdominal wall | Head | 22 mo, dead | Abdominal wall | No therapy    | Miyahara et al[8] |
| 60       | M   | Present | Nodule     | Face, neck | Head | 2 mo, dead | Mesentery      | No therapy    | Miyahara et al[8] |
| 62       | F   | Present | Nodule     | Inflammatory Umbilicus | Tail | 1 yr, dead | Liver, spleen | 5-FU, iOR | Ozaki et al[27] |
| 36       | M   | Present | Nodule     | Umbilicus | Tail    | 5 mo, dead | Peritoneum      | 5-FU, RT | Miyahara et al[8] |
| 77       | M   | Present | Nodule     | Umbilicus | Tail    | 2 mo, dead | Lung           | No therapy    | Miyahara et al[8] |
| 80       | M   | Present | Nodule     | Multiple skin site | Not detail | 5 mo, dead | Para-aortic LN | No therapy    | Wakano et al[28] |
| 78       | M   | Absent  | Nodule     | Umbilicus | Tail    | 4 mo, dead | Peritoneum      | No therapy    | Lesur et al[24] |
| 65       | F   | Present | Nodule     | Chest wall | Head | 8 mo, dead | Liver           | 5-FU, CDPP, IOR | Horino et al[29] |
| 60       | F   | Present | Nodule     | Umbilicus | Tail    | 2 mo, dead | Peritoneum      | Chemotherapy  | Yoneda et al[30] |
| 53       | F   | Absent  | Nodule     | Umbilicus | Tail    | 7 mo, dead | Peritoneum      | Chemotherapy  | Crescenziani et al[31] |
| 64       | F   | Absent  | Nodule     | Abdominal wall | Body | 8 mo, alive | Lung           | Chemotherapy  | Crescenziani et al[31] |
| 75       | M   | Present | Nodule     | Umbilicus | Body    | 6 mo, dead | Liver           | GEM           | Ozakazi et al[32] |
| 82       | M   | Present | Nodule     | Umbilicus | Body    | 5 mo, dead | Peritoneum      | No therapy    | Inadomi et al[33] |
| 73       | F   | Present | Nodule     | Umbilicus | Body    | 6 mo, dead | Peritoneum      | Chemotherapy  | Nagato et al[34] |
| 79       | F   | Absent  | Nodule     | Umbilicus | Tail    | 6 mo, dead | Peritoneum      | No therapy    | Asai et al[35] |
| 65       | M   | Present | Nodule     | Multiple skin site | Body | 1 mo, dead | Liver           | S-FU          | Horino et al[29] |
| 73       | F   | Absent  | Nodule     | Umbilicus | Body    | 6 mo, alive | Supraclavicular LN | GEM | Limmatshurotsakul et al[35] |
| 85       | M   | Present | Nodule     | Temple    | Head    | 3 mo, dead | Lung           | GEM           | Takeamura et al[36] |
| 84       | F   | Present | Nodule     | Umbilicus | Tail    | 4 mo, dead | Liver           | No therapy    | Hayami et al[37] |
| 75       | F   | Present | Nodule     | Umbilicus | Body    | 1 mo, dead | Liver           | No therapy    | Kamata et al[37] |
| 50       | M   | Present | Nodule     | Lateral abdomen | Body | 2 mo, dead | Liver, brain   | GEM, irinotecan | Kimura et al[38] |
| 68       | M   | Absent  | Nodule     | Umbilicus | Body    | 4 mo, dead | Liver, LN       | GEM, UFT-E, RT | Yamashita et al[39] |
| 72       | F   | Present | Nodule     | Umbilicus | Body    | 32 yr, dead | Peritoneum      | GEM, S-1, | Hirahara et al[40] |
| 67       | F   | Present | Nodule     | Lower abdomen | Tail | 3 mo, dead | Liver, LN       | GEM           | Pontinen et al[41] |
| 70       | F   | Present | Nodule     | Lower abdomen | Tail | 4 mo, dead | Liver, peritoneum | GEM | Ozaki et al[42] |
| 81       | M   | Present | Nodule     | Umbilicus | Tail    | 7 mo, dead | Peritoneum      | S-1          | Ozaki et al[42] |
| 59       | M   | Absent  | Nodule     | Umbilicus | Body    | 11 mo, alive | Liver, peritoneum | GEM, S-FU | Ozaki et al[42] |
| 66       | M   | Absent  | Nodule     | Umbilicus | Body    | 18 mo, dead | Liver           | GEM, S-FU | Ozaki et al[42] |
| 58       | F   | Present | Nodule     | Lower abdomen | Body | 10 mo, dead | Liver, lung, peritoneum | GEM, S-FU | Our case |
| 65       | F   | Absent  | Nodule     | Lower abdomen | Tail | 4 mo, dead | Liver, bone, LN | GEM, RT | Our case |

F: Female; M: Male; LN: Lymph node; 5-FU: 5-fluorouracil; RT: Radiation therapy; CDDP: Cis-diammine dichloro platinum; IOR: Intraoperative radiation therapy; GEM: Gemcitabine.
The median survival time (MST) of all patients was 5 mo after diagnosis of cutaneous metastases. The cumulative 1- and 2-year survival rate was 17.5% and 3.5%, respectively (Figure 1A).

Twenty-nine patients (69.0%) had some symptoms, including inflammatory changes such as a flare or sore in 3 patients and the painful or non-tender subcutaneous nodule in 26 patients. Cutaneous metastases were discovered by physical examination without symptoms in the remaining 13 patients (Table 1).

Sites of cutaneous metastases were head or neck in 3 patients, abdomen or chest excluding umbilicus in 7 patients, umbilicus (namely SMJN) in 28 patients and multiple sites in 4 patients. The primary pancreatic lesion was located in the head in 6 patients, body in 11 patients, tail in 22 patients and not recorded in 3 patients (Table 2). Umbilical metastases occurred in 28 patients. Primary pancreatic lesions of umbilical metastases were pancreatic body and tail in 26 patients out of 28. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer ($P = 0.0375$).

Twenty-two patients received chemotherapy after diagnoses of cutaneous metastases. Twelve patients were treated with gemcitabine and 6 with 5-flurouracil (5-FU). Two patients received CRT. The other two patients received other chemotherapeutic agents (Table 1). There was no significant difference between treatment with Gemcitabine and 5-FU (data not shown).

Significant prognostic factors after detection of cutaneous metastases from pancreatic cancer were females and receiving of chemotherapy or CRT among six clinical variables using only univariate analysis (Table 3). The MST of the patients with chemotherapy or CRT was 6.5 mo, significantly better than 4 mo in the patients without any treatment (Figure 1B).
DISCUSSION

Pancreatic cancer is the 5th leading cause of cancer-related death in both men and women in Japan\textsuperscript{[28]}. The majority of pancreatic cancer is advanced at diagnosis (50.5% metastatic vs 8% localized, 25.9% regional spread)\textsuperscript{[29]}. One of the reasons is that pancreatic cancer presents with various incomprensible symptoms. Cutaneous metastases as the first signs of pancreatic cancer were reported in several cases\textsuperscript{[4,14,26,27,30]}. The target of spread of pancreatic cancer substantially includes the regional lymph nodes, liver, lungs, celiac plexus, superior mesenteric vessels, ligament of Treitz, portal vein and skin\textsuperscript{[26]}. The most common metastatic site of cutaneous is the umbilicus (SMJN)\textsuperscript{[4,26]}. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer. Our study revealed that the primary site of SMJN was pancreatic body and tail in 92.9% of patients. Yendluri demonstrated that this might relate to the propensity for tail of pancreas cancers remain asymptomatic until an advanced stage when distant metastasis has been found\textsuperscript{[38]}. Because of potential intercommunications, the umbilicus may gather a variety of tumors. The metastatic cancer cells may travel by retrograde flow from the peritoneal cavity to the umbilicus via the lymphatics of the falciform ligament, the median umbilical ligament of the urachus, the vitello intestinal duct remnant and the obliterated vitelline artery\textsuperscript{[30,31]}. Eventually, tumor micro-embolization through the artery or the portal vein provides a channel for hematogenous implantation and seeding of umbilical tissue\textsuperscript{[2,35]}. Non-umbilical cutaneous metastases are rare but distant spread shows that pancreatic carcinoma can reach all cutaneous tissues via blood or the lymphatic system\textsuperscript{[24]}. There is no significant difference of prognosis between umbilical and non-umbilical metastases in this article (Table 3). Average survival of advanced pancreatic cancer in general is less than 4 mo\textsuperscript{[30]}. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

This study demonstrated significant improvement in median overall survival from 6.5 mo vs 4 mo when some treatment, including chemotherapy alone and CRT, for patients with umbilical metastases from pancreatic cancer compared to no therapy. Several treatments might be performed for patients who had a good enough performance status to receive some treatment, although there is a significant difference in background between these two groups.

In conclusion, prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

**Research frontiers**

The authors evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

**Innovations and breakthroughs**

The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients treated with chemotherapy or chemoradiotherapy (CRT) was 8.5 mo, which was statistically longer in comparison to patients without treatment.

**Applications**

Average survival of advanced pancreatic cancer in general is less than 4 mo. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

**Peer review**

The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

**REFERENCES**

1. Taniguchi S, Hisa T, Hamada T. Cutaneous metastases of pancreatic carcinoma with unusual clinical features. J Am Acad Dermatol 1994; 31: 877-880
2. Gabriele R, Conte M, Egidi F, Borghese M. Umbilical metastases: current viewpoint. World J Surg Oncol 2005; 3: 13
3. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 1993; 29: 228-236
4. Miyahara M, Hanamaka Y, Kawabata A, Sato Y, Tanaka A, Yamamoto A, Ueno T, Nishihara K, Suzuki T. Cutaneous metastases from pancreatic cancer. Int J Pancreatol 1996; 20: 127-130
5. Horino K, Hiraoka T, Kanemitsu K, Tsuji T, Inoue K, Tanabe T, Takamori H, Matsuoka M, Kitamura N. Subcutaneous metastases after curative resection for pancreatic carcinoma: a case report and review of the literature. Pancreas 1999; 19: 406-408
6. Hisamato K, Nishihoya K, Ota T, Matsuoka T. A case of umbilical metastasis from carcinoma of the pancreas [Japanese]. Rinsho Hifu 1987; 41: 1097-1102
7. Taniguchi S, Hisa T, Hamada T. Cutaneous metastases of pancreatic carcinoma showing unusual clinical features: A case report and review of literature [Japanese]. Hifu 1993; 35: 727-730
8. Ohashi N, Iizumi Y, Komatsu T, Izaki K, Kitamura K. Two cases with metastatic skin cancer originally from pancreatic carcinoma [Japanese]. Skin Cancer 1995; 10: 117-121
9. Nakano S, Narita R, Yamamoto M, Ogami Y, Osuki M. Two cases of pancreatic cancer associated with skin metastases. Am J Gastroenterol 1996; 91: 410-411
10. Lesur G, Bergeron AM, Turner L, Dupuy P. [Peritoneal carcinoma with cutaneous metastases in an endocrine tumor of the pancreas]. Ann Med Interne (Paris) 1997; 148: 326-327
11. Yoneda Y, Tawara J, Takayama Y, Nagahara H, Shiratori K. Two cases of umbilical metastatic tumor from pancreatic cancer. Report of Sister Mary Joseph’s nodule [Japanese]. J Jpn Pancre Soc 2003; 18: 507-511
12. Crescentini F, Deutsch F, Sobrado CW, Araújo S. Umbilical mass as the sole presenting symptom of pancreatic cancer: a case report. Rev Hosp Clin Fac Med Sao Paulo 2004; 59: 198-202
13. Okazaki M, Hiratsuka M, Okuno S. A case of the pancreas body cancer finded out by a Sister Mary Joseph’s Nodule [Japanese]. Tumor To Sui 2004; 25: 451-453
14. Inadomi T. Sister Mary Joseph’s nodule: a clue to finding pancreatic cancer in a patient previously affected by gastric cancer. Eur J Dermatol 2005; 15: 492-494
15. Toki H, Matsu S, Azuma T, Haraguchi M, Yamaguchi S, Kanematsu T. Pancreatic cancer with umbilical metastases (Sister Mary Joseph’s Nodule) [Japanese]. Acta Medica Nag-
Horino K et al. Cutaneous metastases secondary to pancreatic cancer

16 Nagato M, Manabe M, Umebayashi Y. A case of Sister Mary Joseph’s Nodule derived from pancreatic cancer [Japanese]. Hifuka No Rinsho 2005; 50: 123-126
17 Asai K, Hiramitsu Y, Yoneda K, Nakura K, Yamada T, Yoshida M. A case of Sister Mary Joseph’s Nodule [Japanese]. Skin Cancer 2007; 22: 136-139
18 Horino K, Kimura M, Nishimura T, Matsusita H, Hirata T, Kawata K. A case of cutaneous metastases from pancreatic carcinoma [Japanese]. Geka 2007; 69: 1097-1100
19 Limmathurotsakul D, Rerknimitr P, Korkij W, Noppakun N, Kullavanijaya P, Rerknimitr R. Metastatic mucinous cystic adenocarcinoma of the pancreas presenting as Sister Mary Joseph’s nodule. JOP 2007; 8: 344-349
20 Takemura N, Fujii N, Tanaka T. Cutaneous metastasis as the first clinical manifestation of pancreatic adenocarcinoma: a case treated with gemcitabine. J Dermatol 2007; 34: 662-664
21 Hayami M, Wakai T, Kaneko K, Maruyama T, Shirai Y, Hatayama K. A case of pancreas cancer derived from Sister Mary Joseph’s Nodule [Japanese]. Niigata Igakkai Zassi 2008; 122: 148-152
22 Kamata A, Iida K. A case of Sister Mary Joseph’s Nodule [Japanese]. Hifuka No Rinsho 2000; 42: 1406-1407
23 Kimura H, Furukawa Y, Kuwada Y, Hananoki M, Matumoto N, Yamamoto M, Fujiwara M. A patient with pancreatic cancer associated with brain and skin metastases [Japanese]. J Jpn Panc Soc 2008; 23: 74-82
24 Yamashita S, Sakon M, Hiura Y, Nakano K, Higaki N, Murakami M, Hayashida H, Kan K, Ichihara T. A case of metastases of umbilicus (Sister mary Joseoh’s nodule) [Japanese]. Gan To Kagaku Ryoho 2008; 35: 2112-2114
25 Hirahara N, Nisi T, Kawabata Y, Inao H, Mitsunari Y, Yano S, Tanaka T. A case of pancreas tail cancer lived for 20 months after chemotherapy by Gemcitabine [Japanese]. Kansai Tansaku 2010; 60: 725-730
26 Pontinen T, Melin A, Varadi G, Khanmoradi K, Chawaproug D, Kung SC, Zaki R, Ortiz J. Cutaneous metastasis of pancreatic adenocarcinoma after kidney transplant: a case report and review of the literature. Exp Clin Transplant 2010; 8: 273-276
27 Ozaki N, Takamori H, Baba H. Sister Mary Joseph’s nodule derived from pancreatic cancer. J Hepatobiliary Pancreat Sci 2011; 18: 119-121
28 Society PCRCoJP. Annual report of national registration of pancreatic cancer patients in 20 years from 1981 to 2000. J Jpn Panc Soc 2003; 18: 101-169
29 Oberstein PE, Saif MW. First-line treatment for advanced pancreatic cancer. Highlights from the “2011 ASCO Gastrointestinal Cancers Symposium”. San Francisco, CA, USA. January 20-22, 2011. JOP 2011; 12: 96-100
30 Yenduluri V, Centeno B, Springett GM. Pancreatic cancer presenting as a Sister Mary Joseph’s nodule: case report and update of the literature. Pancreas 2007; 34: 161-164
31 Powell FC, Cooper AJ, Massa MC, Goellner JR, Su WP. Sister Mary Joseph’s nodule: a clinical and histologic study. J Am Acad Dermatol 1984; 10: 610-615

S- Editor Wang JL  L- Editor Roemmele A  E- Editor Zheng XM