

## Metastasis to the pancreas and the spleen: an increasing diagnostic and therapeutic challenge

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### Abstract

We have reviewed the electronic biopsies database files of the Department of Surgical Pathology, Fundación Jiménez Díaz in Madrid (Spain). In this time period (1998-2010) we have found 3 pancreatic metastasis and 5 splenic metastasis. Two of the pancreatic metastases were originated in clear cell renal cell carcinomas. The last pancreatic metastasis was from a malignant cutaneous melanoma diagnosed and treated 8 years before. As for splenic metastasis, three of them were diagnosed during the abdominal surgery for primary therapy of the tumour (2 ovaries and one endometrium), while the remaining 2 corresponded to metastasis from a lung primary diagnosed 1 year before and a colonic primary diagnosed 6 years before. The patients with splenic metastasis died on the short term with progression of the disease despite resection of the splenic lesions, while the patients with pancreatic metastasis have survived longer.

### Introduction

The changes in oncologic therapies are achieving longer survivals of patients with many tumour types. This increase in survival together with the better sensitivity of imaging techniques can be associated with an increase in the incidence of metastasis on the long-term, what can render diagnostic and therapeutic challenges in the near future. In this sense it is interesting to note the recent increase in the number of reported cases of metastasis to unusual sites, like the pancreas<sup>1-3</sup> or the spleen<sup>4,5</sup> with most series published in the last 5 years. The objective of the present report is to review the cases of pancreatic and splenic metastasis diagnosed at a single center between 1998 and 2010 and to comment on diagnostic and therapeutic aspects in these patients.

### Case Report

The review of the electronic database files of the Surgical Pathology Department of the Hospital Fundación Jiménez Díaz, a tertiary hospital attending over 400.000 people in an urban area of Madrid (Spain), has rendered 156 pancreatotomy specimens (both Whipple procedure and partial resections) and 345 splenectomy ones in the last 12 years. Among these cases we have found 3 cases of pancreatic metastasis (1.9% of the specimens) and 5 cases of splenic metastasis (1.5% of the specimens). Table 1 summarizes the features of the cases.

All the cases of pancreatic metastasis in our series were metachronous with the primary tumour and the time elapsed between therapy of the primary tumour and recurrence was fairly long (8 and 9 years in two patients). It is worth noting that in the three cases the pancreas was the only location of the tumour recurrence and imaging studies revealed no lesions elsewhere in any of the cases. Two patients were asymptomatic, while the third had jaundice and pain that led to a preoperative diagnosis of pancreatic adenocarcinoma. In neither case there was any clinical suspicion of tumour recurrence and the other two cases were diagnosed of neuroendocrine primary pancreatic tumours, despite the biochemical assays failed to show any abnormal hormone secretion. All the patients were surgically treated with a radical or partial pancreatotomy depending on the location of the mass. It is interesting to note that in one patient the lesions were multiple (2 in the head of the pancreas and 1 in the body), while the other was a solitary nodule in the pancreatic tail (Figure 1). Two of the



Figure 1. Computed tomography scan showing a nodule in the tail of the pancreas. The lesion was hypervascular and preoperative diagnosis was neuroendocrine pancreatic tumor.

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patients (both with metastasis from a clear cell renal carcinoma; Figure 2) are doing well and remain well and disease free, almost one year after diagnosis. The third one, who had metastasis from a malignant melanoma, operated 8 years before and who had no previous recurrence of the tumour, died of widespread disease 8 months after Whipple procedure

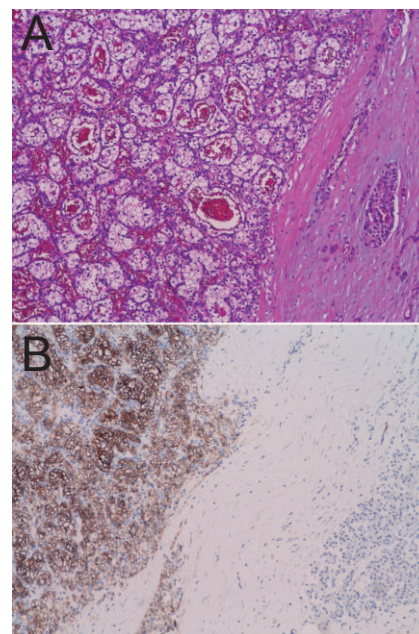


Figure 2. A) Hematoxylin-eosin stained medium power image of the pancreatic metastasis from a clear cell carcinoma. B) Immunohistochemical expression of CD10 confirmed renal origin. Note the presence of pancreatic endocrine normal cells at the periphery of the metastatic nodule (H-E, x 200; Immunohistochemistry for CD10).

**Table 1. Summary of the cases**

| Location                  | Sex/age   | Primary   | Therapy of the primary tumour  | Time since diagnosis of the primary | Presenting symptoms                             | Preoperative diagnosis of the metastasis | Therapy   | Outcome  |
|---------------------------|-----------|---|--|-------------------------------------|---|--|---|--|
| Head of the pancreas      | Female 58 | malignant melanoma, Clark level 4 of the leg                              | Surgery: resection and lymphadenectomy (0/18 lymph nodes affected by tumour) | 8 years                             | Jaundice and pain                               | Pancreatic adenocarcinoma                | Cephalic duodeno-pancreatectomy (whipple procedure)       | Good evolution surgery; dead of widespread disease 8 months after surgery    |
| Head and body of pancreas | Female 71 | Renal clear cell carcinoma (left side) pT1a N0 M0                         | Surgery: radical nephrectomy   | 15 months                           | Incidental finding during surveillance          | Neuroendocrine pancreatic tumors         | Subtotal pancreatectomy                                   | Good evolution after surgery; alive and disease free 8 months after surgery  |
| Tail of the pancreas      | Female 53 | Renal clear cell carcinoma pT1b N0 M0                                     | Surgery: radical nephrectomy   | 9 years                             | Incidental finding during surveillance          | Neuroendocrine pancreatic tumor          | Resection of the tail of the pancreas and splenectomy     | Good evolution after surgery; alive and disease free 12 months after surgery |
| Spleen                    | Female 75 | Ovarian serous Poorly differentiated carcinoma                            | Surgery: omentectomy, splenectomy, hysterectomy and bilateral oophorectomy   | Synchronous with the primary        | Involvement found during surgery of the primary | None                                     | Splenectomy and chemotherapy                              | Dead of disease 9 months after surgery                                       |
| Spleen                    | Female 74 | Ovarian high grade carcinoma  | Surgery: omentectomy, splenectomy, hysterectomy and bilateral oophorectomy   | Synchronous with the primary        | Involvement found during surgery of the primary | None                                     | Splenectomy and chemotherapy                              | Dead of disease 15 months after surgery                                      |
| Spleen                    | Female 77 | High grade papillary serous carcinoma of probable endometrial origin      | Surgery: splenectomy, hysterectomy and bilateral oophorectomy                | Synchronous with the primary        | Involvement found during surgery of the primary | None                                     | Splenectomy chemotherapy                                  | Dead of disease 42 months after surgery                                      |
| Spleen                    | Male 72   | Squamous cell carcinoma of the lung                                       | Chemotherapy with good response  | 14 months                           | Incidental finding during surveillance          | Metastasis vs. lymphoma                  | Splenectomy   | Dead of disease 12 months after surgery                                      |
| Spleen                    | Male 63   | Enteroid well-differentiated adenocarcinoma of the large intestine T3N1M0 | Surgery and chemotherapy   | 6 years                             | Imaging finding                                 | Metastasis                               | Splenectomy with resection of isolated hepatic metastasis | Dead of disease 8 months after splenectomy                                   |

(Figure 3). However, at the time of pancreatotomy both imaging neither studies nor clinical examination revealed metastases elsewhere and they developed later in the course of the disease and eventually killed the patient.

The history of splenic metastasis seems quite different. Three of our cases were synchronous with the primary tumours, located two in the ovaries and one in the endometrium. All these women had widespread disease in the abdominal cavity at the time of the primary surgery and died of disease on the short-medium term, despite aggressive resection and postoperative chemotherapy. Only two of the splenic metastases in our series were metachronous with the primary tumour. One was a metastasis from an squamous cell carcinoma of the lung, treated with chemotherapy 14 months earlier, that recurred as an isolated splenic mass (Figure 4). The second was a M. Jesúscolonic adenocarcinoma that recurred 6 years after colectomy as hepatic and splenic metastasis (Figure 5). In both cases surgery was deemed necessary both to confirm diagnosis and to improve the patients' outcome. However, despite surgical therapy and postoperative chemotherapy both patients died within one year.

## Discussion

Metastasis to unusual sites are being increasingly reported,<sup>6,7</sup> a fact that can be in part explained by: i) the longer survival of oncologic patients related to improved therapies; ii) the better standardized oncological follow-up after primary therapy; iii) the improved sensitivity of the imaging techniques; iv) and a more aggressive surgical and oncological attitude in cases with metastasis. In this report we have reviewed the metastasis to the pancreas and the spleen in a tertiary hospital in Madrid (Spain).

Our experience seems to fit the most recently reported reviews on this topic. In a recent editorial by Zerbi *et al.*<sup>6</sup> the authors emphasize the dramatic increase in the incidence of pancreatic metastasis since 2008. According to their review pancreatic metastasis represent 2% of all pancreatic tumours (1.9% in our series). Prognosis after resection can be related to the tumour type and the therapeutic options after it. The most frequent type is renal clear cell carcinoma (RCC), as already described by other authors.<sup>8</sup> It is followed by colorectal cancer, melanoma and sarcoma, but in the literature there are reports of metastasis from almost any tumour type, including lobular breast carcinoma and even as the first symptom of an occult primary.<sup>9</sup>

One peculiar feature of RCC is the long latency between diagnosis of the primary

tumour and appearance of the pancreatic metastasis. In one of our patients 9 years elapsed between radical nephrectomy and pancreatic metastasis. In this time the patient remained disease-free with no further therapy. Although metastasis from RCC have been described as hypervascular with imaging techniques and both our cases showed this imaging feature, preoperative diagnosis in our patients was neuroendocrine pancreatic tumour, a much more frequent occurrence. In this sense, we should take into account the possibility of metastatic spread from a primary tumour, independently of the time elapsed since the first malignant lesion.

There has been much controversy in the literature regarding resection for pancreatic metastasis. In a recent systematic review of over 400 patients with pancreatic metastasis of RCC,<sup>10</sup> a 5-year survival over 70% was found after resection; this figure seems to justify metastasectomy in patients able to tolerate pancreatic resection, for it equates the results obtained after hepatic or lung metastasectomy, a therapeutic approach which is now widely accepted in the oncologic literature. In this sense it would be useless to perform fine needle aspiration cytology of pancreatic masses suspicious of metastasis, as therapy would be surgical, mainly when there is no metastatic spread elsewhere. Most authors recommend standard radical pancreatic resection,<sup>11</sup> as the experience of some authors employing atypical more conservative resections describes a 29% rate of local recurrences.<sup>12</sup> However it is worth noting that, to date, there are no reports comparing surgery to the modern biological therapies that are increasingly used in renal carcinomas. If diagnosis of metastasis could be confirmed, the chance to employ these new drugs could avoid surgery in responding cases and reduce the important morbidity and mortality related to pancreatic surgery. Nevertheless, experience regarding this therapeutic option is lacking so far.

Surgical results seem not to be changed by multiplicity of the metastatic nodules within the pancreas, a fact which was considered rare, but reaches 39% of the cases in some recent reviews.<sup>13</sup> One of our patients showed this pattern of involvement with three metastatic nodules that obliged to perform a subtotal pancreatectomy from which she recovered uneventfully.

Prognosis after surgery is not as good for the other histologic tumour types. Metastatic malignant melanoma behaves very poorly according to most reports and prognosis is bad, with a median survival time of 14 months, even when metastasis were limited to the pancreas. However, the lack of alternative therapeutic options for this tumour and the possible symptoms associated with it can justify surgery as a valid alternative, with palliative or

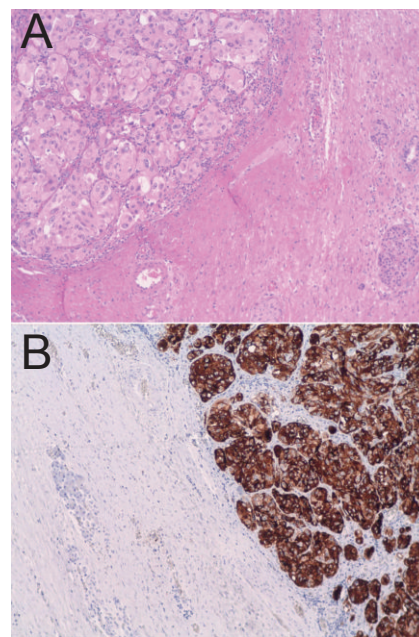


Figure 3. A) Hematoxylin-eosin stained medium power image of the pancreatic metastasis from malignant melanoma. B) The tumor expressed HMB-45 and S-100 protein (A, H-E, x 200; B, Immunohistochemistry for HMB-45).

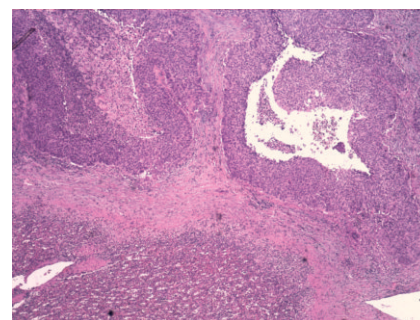


Figure 4. Hematoxylin-eosin stained medium power image of the splenic metastasis from squamous cell carcinoma. Note normal splenic tissue in the left bottom of the image (H-E, x 200).

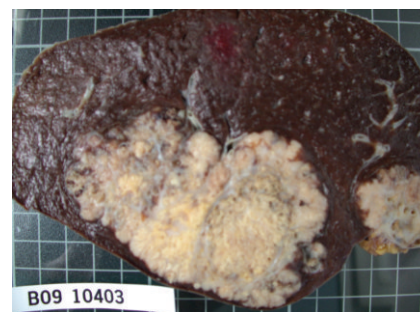


Figure 5. Gross photograph showing the large splenic nodule with a smaller satellite one, corresponding histologically to metastases from an enteroid adenocarcinoma of the large intestine.

curative intention, as happened in our case.

The experience with other tumours is very scarce, but recent reviews indicate surgery is justified for isolated pancreatic metastasis from colonic tumours and sarcomas of the gastrointestinal stromal tumour (GIST) type, but not for lung tumours. However, in these cases long survival is only achieved when postoperative chemotherapy or molecular targeted therapy are employed.

The incidence of splenic involvement in autopsy series from oncologic patients has ranged from 2-7%.<sup>14</sup> However, less than 150 cases of isolated splenic metastasis undergoing splenectomy have been reported to date. A recent review by Gatenby et al. reports 21 cases from different primaries, mainly ovary, malignant melanoma and pancreas.<sup>7</sup> As it is also the case in pancreatic metastasis, metastasis to the spleen can appear long after diagnosis and therapy for the primary tumour.<sup>5</sup> In our series we have found two cases originating in the ovaries and one in the endometrium, both metachronous with the primary tumour, and two metachronous ones from the lung and the colon. The lung seems an infrequent origin for splenic metastasis and less than 10 cases have been published in the world literature;<sup>14,15</sup> the interval between diagnosis and metastatic involvement has widely varied from 0 to 8 years. Prognosis in these cases seems poor, despite further therapy. The literature indicates prognosis is better for metachronous metastasis over synchronous ones and also for metastasis originating in the colon and the ovary. Splenectomy seems to be clearly indicated for solitary lesions, even when suspicious of metastasis, due to the low incidence of complications of this type of surgery and also to the need to confirm diagnosis to decide further therapy. We should not forget that malignant lymphoma can also arise as a solitary splenic nodule and imaging does not allow differential

diagnosis of the histology of the lesions. In our series prognosis of the patients with splenic metastasis has been uniformly poor. Nevertheless, it seems an improved outcome may be seen in patients for whom there were effective adjuvant chemotherapeutic options, low probability of other metastatic disease and less aggressive tumour biology.

## Conclusions

In this report we review the cases of isolated pancreatic and splenic metastases in our tertiary hospital. Our experience seems to fit to the reported literature regarding tumour types and outcome of the patients. According to the present literature metastasectomy is indicated to improve prognosis of these patients.

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