CASE REPORT

Long-Term Survival after Resection of Pancreatic Ductal Adenocarcinoma with Late Metachronous Pulmonary Metastasectomy

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ABSTRACT

Objective Pancreatic ductal adenocarcinoma has a five year survival rate of 20% following radical surgical resection. The aggressive tumor biology and heterogenous nature of pancreatic ductal adenocarcinoma results in metastatic spread which further decreases overall survival. We report a patient who successfully underwent a pulmonary metastasectomy five years after the resection of a pancreatic ductal adenocarcinoma originating from an intraductal papillary mucinous neoplasm. **Case report** A sixty-one-year-old male underwent a pancreaticoduodenectomy with vein resection for a locally advanced pancreatic ductal adenocarcinoma. The origin of the tumor was from an intraductal papillary mucinous neoplasm. The patient had an uneventful recovery and follow up showed no sign of disease recurrence. Five years after the primary resection, the patient experienced rapid weight loss despite adequate nutrition. A computed tomography scan revealed a 22 x 16 mm lesion in the upper lobe of the left lung. The patient underwent a thoracoscopic resection of the lesion and histology confirmed this to be a metastasis from the primary pancreatic ductal adenocarcinoma. A period of eight years has passed since the primary resection and the patient continues to do well. **Conclusion** We here present a case of long term survival of a patient who underwent a metachronous pulmonary metastasectomy after pancreatic resection for a pancreatic ductal adenocarcinoma originating from an intraductal papillary mucinous neoplasm. This highlights the fact that selected patients may benefit from resection of solitary pulmonary metastasis of pancreatic ductal adenocarcinoma. While this adds further complexity and dynamism to oncologic therapy it is an important step towards individualized care.

INTRODUCTION

Pancreatic ductal adenocarcinoma has a five year survival rate of 20 % following radical surgical resection [1]. The majority of patients (~80%) are unresectable at the time of diagnosis, either due to loco-regional or metastatic disease [2]. This poor prognosis is attributed to the absence of symptoms in early pancreatic cancer combined with aggressive tumor biology and rapid disease progression [2, 3] and is the basis for a prevailing nihilism regarding treatment of PDAC. However, due to the heterogenous nature of PDAC a confirmed diagnosis does not necessarily confer a poor prognosis. We report a patient who successfully underwent a pulmonary metastasectomy five years after the resection of a PDAC having originated from an intraductal papillary mucinous neoplasm (IPMN).

CASE REPORT

A sixty-one-year old male presented to the clinic with diarrhea and marked weight loss of 14 kg over six months. A CT scan identified a 36 mm tumor in the head of the pancreas with a 3 cm, 50% circumferential involvement of the superior mesenteric vein **(Figure 1)**. There was no evidence of metastatic disease and thus the patient underwent a pancreaticoduodenectomy with *en bloc*

Figure 1. Preoperative CT showing a 36 mm tumor in the head of the pancreas.

resection of the involved portion of the mesenteric vein. There were no perioperative or postoperative complications and the patient was discharged on postoperative day 15. The final pathology report identified the tumor as a well differentiated ductal adenocarcinoma having originated from a pancreaticobiliary intraductal papillary mucinous neoplasm (IPMN). All of the 24 examined lymph nodes were negative for cancer. Final pathology thus staged the tumor as a T3N0Mx. At this point the patient did not wish for further adjuvant therapy.

The patient continued to do well on follow up clinic visits. After a period of five years the patient once again developed similar symptoms as his initial presentation with fatigue and weight loss. A computed tomography (CT) scan of the chest now showed a 22 x 16 mm cyst like lesion with solid components in the apical region of the upper lobe of the left lung **(Figure 2)**. At this point it was unclear whether the lesion was a primary lung cancer or a pancreatic metastasis. As the patient was in good physical condition, the decision was made to excise the pulmonary lesion. This was performed with a video-assisted thoracoscopic lobectomy. The hospital stay was uneventful following the procedure and the patient was discharged on post-operative day seven.

Histology of the pulmonary lesion showed characteristics of adenocarcinoma. On immunohistochemistry, tumor cells stained positive for CDX2, SMAD4, CK7, and negative for CK20. A weak, focal positivity was noted for TTF-1 which would normally indicate a primary pulmonary malignancy. However further analysis revealed PDX1 and Villin positivity which together with the histological morphology identified the lesions as a metastasis from the primary PDAC. It was again recommended that the patient should undergo adjuvant treatment with gemcitabine. However, the patient refused further treatment. Instead it was decided to continue monitoring the patient with scheduled clinic visits and CT examinations every 6 months. Subsequently, the patient regained his weight and his gastrointestinal symptoms improved. He continues to do well three years after his pulmonary resection

Figure 2. CT examination 5 years following the primary tumor resection showing a 22 mm lesion in the left upper lobe of the lung.

and subsequent CTs have shown no signs of recurrent intraabdominal or intrathoracic disease.

DISCUSSION

We here report a patient with ductal pancreatic carcinoma who has survived over eight years despite metastasis to the lungs five years after the primary resection. While five years is the standard period of follow up after pancreatic cancer surgery, recurrences after this time period are known to occur [4].

There have been no signs of liver metastasis despite a pulmonary metastasis during the eight years of follow-up; an unexpected phenomenon from a biological point of view [3]. This would either suggest that the tumor had spread through the caval venous system or through lymphatics. Another theory is that the lesion in the lung was in fact a primary pulmonary malignancy with a similar immunohistochemical pattern as the primary tumor. Such a "fingerprint similarity" is however unlikely considering that the pattern was not typical for a primary lung cancer. Moreover, the patient is not a smoker and has no other risk factors for lung cancer.

Another interesting fact to be considered is that the PDAC arose from an IPMN. While biological studies with these types of cancer are limited, it has been shown that PDAC derived from IPMN may have favorable biological characteristics [5-7]. The pattern of metastasis has also not been completely described for these types of tumors. However, in our case the primary cancer was symptomatic and was not at an early stage (36 mm in largest diameter with vascular involvement). Therefore, it is difficult to explain why there should be a single pulmonary metastasis without liver metastasis or local recurrence thus highlighting the unique biology of our patient's cancer.

It is well documented that patients with post-operative recurrence in the form of liver metastases have significantly shorter survival rates than patients with local recurrence [8]. The biology of pulmonary metastases is less known, but it has been reported that among long term survivors (>five years) following pancreatic resection for PDAC, the most common site of disease recurrence may be the lung [9, 10]. A case series by Arnaoutakis *et al.* [11] included patients with isolated pulmonary metastases from PDAC. They demonstrated significantly higher survival rates in patients who underwent successful pulmonary metastasectomies compared to those that did not, 51 *vs.* 23 months respectively. While a certain level of selection bias may be reflected in this finding, the average survival following pulmonary lobectomy was 19 months.

Kitasato *et al.* [12] also reported a case of pulmonary adenocarcinoma 13 years after a curative resection for pancreatic cancer. The pulmonary metastasis from a PDAC described in the case was also a well differentiated adenocarcinoma with TTF-1, CK20 negative and CK7 positive. Another case of pulmonary metastasis originating from the pancreas, reported by Shah *et al.* [13], was also positive for CK7 and negative for CK20.

A major limitation to the present case is that serum CA19-9 levels were not obtained prior to the pancreaticoduodenectomy or the pulmonary metastastectomy. This could have added significant value regarding the prognosis of the patient. Okusaka *et al*. reported that in isolated cases of lung recurrences following pancreatic ductal adenocarcinoma, a CA19-9 level above 185 was predictive of worsened outcomes [14]. Additionally, the patient's adenocarcinoma originated from an IPMN and it has been described that elevated levels of CA19-9 indicates high risk malignant disease [15, 16]. At the time of the patient's initial operation, it was not standard protocol at our institution to routinely check serum CA19-9.

In current practice patients with synchronous presentation of pancreatic cancer and pulmonary metastasis are not considered eligible for surgery [17]. A retrospective study by Porok *et al.* [18] found that out of 374 patients resected for PDAC 183 (49%) had indeterminate pulmonary nodules at the time of diagnosis. Of these, only 29 (16%) progressed to clinically recognizable metastatic lung disease. Interestingly the presence of lung metastasis did not significantly affect survival. Thus, the tumor biology of PDAC – and especially some aspects of its metastases – is complex in comparison to other forms of malignancy. Studies have shown genetic differences in cancer cells of hepatic and peritoneal metastases, both originating from the pancreas [19]. As such it is highly likely that pulmonary metastases have a distinct tumor biology and as indicated by other studies, it may also be possible that PDAC metastatic to the lung carries a better prognosis.

CONCLUSION

To conclude, patients that undergo solitary pulmonary metastasectomy after PDAC seem to have an improved survival over patients with other sites of metastasis. While these studies are prone to selection bias, the finding is thought provoking. It highlights the need to elucidate factors that can select patients who might benefit from such a procedure. With an increasing recognition of the heterogeneity of PDAC, it will be important to tailor therapeutic approaches following a careful selection of patients. While this will add further complexity and dynamism to oncologic therapy it is an important step towards individualized care.

Consent and Conflicts of interest

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