Synchronous primary adenocarcinoma of the lung and pancreas: a case series and review of the literature

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Aim: The frequency of pancreatic cancer in association with cancer of other organs ranges from 1 to 20%, with the most common ones being gastric, colon, thyroid and genitourinary. The presence of synchronous lung and pancreatic cancers is extremely rare. **Case series:** Two patients with extensive smoking history and variable presentations were found to have simultaneous lung and pancreatic masses both lesions being different histologically and on immunohistochemical staining. After individualized treatment plans, the first patient remains free of disease and the second patient is being treated with a palliative intent. **Conclusion:** The early recognition and treatment is important as there exists a significant survival difference in patients who have synchronous primaries as opposed to those with metastatic pancreatic adenocarcinoma.

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Practice points

- When metastatic disease is suspected radiologically, a biopsy is imperative prior to initiating therapy.
- Morphological and immunohistochemical assessment including TTF-1, napsinA, CDX2, CK20 together with KRAS mutational analysis has high diagnostic utility to differentiate the origins in synchronous malignancies.
- The early recognition and treatment of synchronous lung and pancreatic malignancies is important as there exists a significant survival difference as compared with those with metastatic pancreatic adenocarcinoma.
- Early diagnosis of two limited staged primaries can be treated with a tailored personalized treatment plan with good outcomes.
- In patients with synchronous primaries the prognosis primarily depends on the stage and biology of the more aggressive malignancy.
- Extensive smoking history, genetic contributors and chronic inflammation could potentially contribute to increased risk of synchronous primaries.

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KEYWORDS

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- synchronous primaries

The incidence of multiple primary malignancies appears to be increasing due to increasing overall life expectancy, better cancer therapies and more sensitive modalities for detection. The reported frequency of multiple synchronous primary tumors is 1–3% [1]. The frequency of pancreatic cancer in association with cancer of other organs is estimated to range from 1% to as high as 20% [2], with the most common secondary malignancies being gastric, colon, thyroid and genitourinary [3]. Moreover, most of the lung and pancreatic cancer occurring synchronously are associated with tobacco use [4]. Common factors like extensive smoking history, dietary factors, co-morbidities, genetics and chronic inflammation could be contributing to the occurrence of synchronous malignancies to some extent. The presence of synchronous lung and pancreatic cancers is extremely rare with only four reports in the English literature [2,5]. In one of the largest studies in a Japanese cohort of 337 resected lung cancer cases over 7 years, there were 24 cases of multiple primaries. Only two cases of primary lung and pancreas were noted [5]. In the same study the histology of lung cancer in 13 cases of synchronous double malignancies were adenocarcinoma in six, squamous cell carcinoma in two, large cell carcinoma in three, small cell carcinoma in one and adenosquamous cell carcinoma in one [5]. Pancreatic cancer is usually rapidly fatal with a median survival after surgical resection of only 14–20 months [6] and a 5-year overall survival rate of 9% for all stages [7]. Some patients can have a prolonged clinical course and development of late metastasis. As per one study of pulmonary resections for isolated pancreatic adenocarcinoma metastases, the median time from pancreatectomy to identification of the first pulmonary nodule on imaging was 29 months and to metastectomy was 34 months [8]. Even though the diagnosis of metastatic disease is based on radiographic evidence of more than one site of involvement, the possibility of synchronous lesions needs to be excluded.

Here we present our experience with two patients with extensive smoking history who were diagnosed with synchronous lung and pancreatic primaries and their treatment courses.

Case series

• Case 1

Patient A is a 72-year-old female with previous history of metachronous bilateral breast cancer treated with a lumpectomy, chemotherapy and

radiation (right breast 20 years ago and left breast 10 years ago) and a 30-pack-year smoking history who presented with worsening cough, unintentional weight loss and fatigue to her primary care provider. A chest x-ray identified an 8.5 × 12.5 mm nodule in left upper lobe of the lung which was confirmed on a CT thorax scan (Figure 1A). A positron emission tomography-computed tomography scan done for staging demonstrated metabolic uptake in a pancreatic body/tail mass (standardized uptake value 10.0) with no uptake seen in lung nodule (Figures 1B, 2A & 2B). There were no mediastinal/abdominal lymph nodes or other metastatic disease. Endoscopic evaluation of the pancreatic mass confirmed a 2 × 1.9 cm pancreatic mass with no involvement of superior mesenteric or celiac artery and biopsy confirmed this to be an adenocarcinoma on histopathology (Figure 3A & B). Biopsy of the lung nodule confirmed this to be an adenocarcinoma on histopathology (Figure 4A): morphologically and immunohistochemically different from the pancreatic mass. The lung adenocarcinoma immunohistochemically stained positive for TTF-1 (Figure 4B) which is expressed in lung adenocarcinomas and thyroid carcinomas but not in adenocarcinomas arising from other sites, routinely used to distinguish a primary lung cancer from a lung metastasis. The lung adenocarcinoma also stained positive for napsin A, TCK and CK 7 all of which show positivity in lung adenocarcinoma and was negative for GATA 3, a transcription factor with low frequency of expression in lung adenocarcinoma. Although the pancreatic adenocarcinoma stained positive for Villin (Figure 3C), a microfilament-associated, actin binding protein typical of brush-border microvilli seen in GI tract adenocarcinomas, negative in normal lung columnar epithelium and their associated adenocarcinoma. The pancreatic adenocarcinoma also stained negative for TTF-1 (Figure 3D). Kras mutational analysis was not evaluated since the morphological and immunohistochemical patterns were clearly distinct on the lung and pancreatic biopsies. Also, the lung biopsy showing strong positivity for TTF-1, napsin A, CK-7, being negative for villin, demonstrated it did not have any component of being an enteric phenotype and was not likely to be a primary pulmonary enteric adenocarcinoma. The treatment plan was decided with input from our multidisciplinary thoracic and gastrointestinal oncology tumor boards. Her early stage lung adenocarcinoma was treated

with stereotactic body radiation therapy to a dose of 50 Gy in four fractions. The pancreas was treated with neoadjuvant chemoradiation with radiosensitizing capecitabine to a dose of 50.4 Gy in 28 fractions. The patient had a radiological complete response on imaging and

underwent a successful distal pancreatectomy with splenectomy. The final pathologic staging at surgery was pT1N0pMx, out of 10 lymph nodes examined, 0 were involved. Despite the small size of the pancreatic tumor neoadjuvant chemoradiation was preferred to help develop a surgical

Figure 1. Imaging for the lung nodule. (A) Computed tomography of thorax showing left upper lobe lung nodule. (B) Positron emission tomography-computed tomography showing mildly hypermetabolic lung nodule.

Figure 2. Imaging for the pancreatic mass. (A) Computed tomography of abdomen/pelvis with axial, coronal and sagittal sections showing pancreatic body/tail mass with pancreatic ductal dilatation. (B) Positron emission tomography-computed tomography showing increased uptake in the area of pancreatic body-tail mass.

Figure 3. Histopathology for the pancreatic mass. (A) Histopathology: Pancreatic ductal adenocarcinoma within lymphovascular spaces. **(B)** Histopathology: Pancreatic ductal adenocarcinoma, high power. **(C)** VILLIN STAIN: Positive in pancreatic adenocarcinoma. **(D)** TTF-1 STAIN: Negative in pancreatic adenocarcinoma.

plane overlying the superior mesenteric vein or the portal vein and splenic vein confluence for effective resection and to avoid intraoperative venous reconstruction. In addition, in a patient with synchronous primaries the authors wanted to evaluate the risk of surgery after confirmation that there was no evidence of micro metastatic disease and hence neoadjuvant therapy was initiated. Currently, the patient has been followed for 1 year and 5 months with surveillance positron emission tomography-computed tomography or CT scans every 3 months and has had no evidence of loco/regional/distant disease. Comprehensive genetic testing was performed on follow-up which included analysis of the APC, ATM, BRCA 1, BRCA 2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11 and TP53 genes. This revealed a mutation in a variant of BRCA 2 called p.G2609V which is of uncertain significance and may or may not affect the function of the protein encoded by the BRCA2 gene. Testing of this variant may be offered free of charge to her family members with a history of malignancy by a laboratory as

part of their research to obtain more information about this variant.

• Case 2

Patient B is a 77-year-old male with a 50-pack year smoking history who presented with non-specific gastrointestinal symptoms including weight loss, early satiety and bloating to his gastroenterologist who he followed for a previous episode of pancreatitis. Imaging studies demonstrated a 4.7×2.8 cm pancreatic head mass (Figure 5). Endoscopic evaluation confirmed the mass and biopsy confirmed this to be an adenocarcinoma. It was staged as locally advanced with possible superior mesenteric vein involvement and involved multiple mesenteric and portal lymph nodes as well. As a part of the initial staging, a computed tomography (CT) of the thorax identified a 3.6×3.6 cm right lower lobe lung mass with subcarinal lymphadenopathy, making the lung cancer stage IIIA (Figure 6). A CT-guided biopsy of lung mass showed moderate to poorly differentiated adenocarcinoma which was morphologically and

Figure 4. Histopathology for the lung nodule. (A) Histopathology: lung adenocarcinoma with acinar features. **(B)** TTF-1 STAIN: positive in lung adenocarcinoma.

immunohistochemically different from the pancreatic adenocarcinoma. The lung mass stained positive for CK7, TTF-1, napsin A and negative for p40, p63 which are both highly sensitive and specific for pulmonary squamous cell carcinoma. Due to the patient's multiple comorbidities, the decision was made to treat the patient with palliative chemotherapy with gemcitabine and nab-paclitaxel which has efficacy in both lung and pancreatic adenocarcinomas. He was also evaluated for hyperbilirubinemia with an ERCP which showed malignant stricturing of the common bile duct with proximal dilatation and a metallic stent was placed for the same. The patient has so far received five cycles of treatment and tolerated them well, except for some thrombocytopenia (nadir 17 k/mm^3) leading to subsequent dose reduction of gemcitabine to

800 mg/m^2 and switching of schedule from the usual day 1, 8, 15 to biweekly. His repeat CT chest/abdomen/pelvis showed decreased size of pancreatic mass to $4.1 \times 2.4 \text{ cm}$ and reduction in size of lung mass to $1.9 \times 1.4 \text{ cm}$. He was also given concurrent neulesta for support and continues to do well during these 8 months of follow-up. He developed a right lower extremity nonocclusive deep vein thrombus during the treatment course and was started on anticoagulation. Assuming he continues to have a response, we will plan to treat him with chemoradiation therapy to the lung and/or pancreas.

Discussion

The above cases illustrate the varied nature of presentation of synchronous pancreatic and lung adenocarcinomas. Early recognition and

Figure 5. Computed tomography abdomen axial/coronal/sagittal sections showing pancreatic head mass causing obstruction and massive dilation of the pancreatic duct.

Figure 6. Computed tomography of the chest showing right lower lung lobe mass.

treatment is important as there exists a significant survival difference in patients who have synchronous primaries as opposed to those with metastatic pancreatic adenocarcinoma [9]. The most common site of distant metastasis for pancreatic adenocarcinoma is the liver, followed by the peritoneum and then the lung [9–12]. Thus synchronous lung masses cannot be assumed metastatic unless proven histopathologically. In patients with synchronous primaries which include a pancreas cancer, the prognosis primarily depends on the stage of the pancreatic carcinoma. In the cases where resection can be performed, the average survival rate is

23–36 months. The overall 5-year survival rate is about 9–10%, although this can rise as high as 20–35% if the tumor is removed completely and when cancer has not spread to lymph nodes as per the American Cancer Society [7]. Thus, histopathologic confirmation is crucial in these patients for tailored treatment recommendations. In our experience, the detection of two limited stage primaries led to a tailored personalized treatment plan with good early outcome in one patient.

K-RAS mutation analysis has been used in the literature to identify origin in cases of synchronous ovarian and pancreatic lesions,

as ovarian mucinous adenocarcinoma or pancreatic adenocarcinoma. Different K-RAS mutations were found in both, pancreas being G12V and ovarian being G12D [13]. Immunohistochemical assessment of TTF-1, napsin A, CDX2, CK20 together with KRAS mutational analysis may have diagnostic utility. The presence of KRAS G12C mutation shows to have 96% specificity and PPV for lung adenocarcinoma, whereas G12R has 99% specificity for pancreatic cancer with a PPV of 86%. TTF-1 and napsin are associated with primary lung adenocarcinoma whereas CK20 and CDX2 favor pancreatic adenocarcinoma, however these stains have limited sensitivity and specificity [14].

Conclusion

Lung and pancreatic synchronous malignancies have extremely low incidence and have a better prognosis when diagnosed early than metastatic pancreatic adenocarcinomas. Hence

when metastatic disease is suspected, biopsy is imperative to confirm this prior to initiating therapy. Patients with synchronous primaries can be treated aggressively per the stages of the individual primaries.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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