Case Reports in Oncology

Case Rep Oncol 2023;16:988–998
DOI: 10.1159/000531841
Received: April 24, 2023
Accepted: June 20, 2023
Published online: September 22, 2023

Case Report

Isolated Pancreatic Metastasis from a Lung Adenocarcinoma Primary: A Case Report and Literature Review

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Keywords
Isolated pancreatic metastasis · Solitary metastasis · Pancreatic metastasis · Lung primary · Unusual metastasis

Abstract
Isolated pancreatic metastasis is a rare occurrence and is commonly misdiagnosed as primary pancreatic malignancy. We present a case of a 65-year-old female patient with a history of stage IIIA lung adenocarcinoma, who developed significant epigastric pain 27 months after diagnosis and treatment of a primary lung adenocarcinoma. This patient was found to have a pancreatic head lesion initially suspected to be a primary pancreatic neoplasm but eventually discovered to be a metastatic lesion from the previously treated primary lung adenocarcinoma.

Introduction

Treatment of advanced and metastatic lung cancer places significant emphasis on molecular testing, with the development of specific guidelines in this regard. These molecular tests allow the possibility for targeted therapies directed at specific molecular abnormalities driving carcinogenesis. In non-small cell lung carcinoma (NSCLC), the most common driver mutations involve exon 19 deletions and exon 21 point mutations. Tyrosine kinase inhibitors stand as the first line of defense for these epidermal growth factor receptor (*EGFR*) gene mutations [1, 2].

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In more recent times, several studies have shown that incorporation of immune checkpoint inhibitors (ICIs) into treatment regimen confers improved outcomes including survival and treatment response outcomes [3, 4]. Moreso, ICIs are heralded as the first-line monotherapy in advanced and metastatic NSCLC with high checkpoint expression (>50%) and without targetable EGFR or anaplastic lymphoma kinase mutations [5]. Even in the absence of immune checkpoint expression, survival benefits have been shown with combination therapy including an ICI along with traditional chemotherapy, with or without antiangiogenesis drugs, compared with standard chemotherapy regimen alone [6]. Nevertheless, the use of these relatively newer drugs is limited by similar constraints associated with traditional chemotherapy, notably, patient tolerability due to adverse effects, which may in turn limit the ability for long enough treatment to achieve substantial response [7, 8].

Extra-thoracic metastasis of lung cancer is most commonly to the bones, liver, adrenal gland, and intrabdominal lymph nodes [9]. Pancreatic metastasis is commonly associated with diffuse metastatic disease [10, 11] and when metastasis occurs from a lung primary, it is most frequently from small cell lung cancers [12]. Pancreatic metastasis from lung primaries is a rare occurrence, with one study showing that only 1% of non-small cell lung cancers result in pancreatic metastasis [13]. This case concerns a patient with a primary lung adenocarcinoma with an isolated and solitary metastatic pancreatic head mass.

Case Report

A 65-year-old female patient with a history of stage IIIA lung cancer diagnosed 27 months prior, presented to the oncology clinic with reports of abdominal pain and a pancreatic head lesion found on abdominal and pelvic computed tomography (CT) scan at a non-affiliated hospital in August 2022.

The patient had a substantial smoking history of greater than 40 pack years, along with hypertension, hypothyroidism, and dyslipidemia. Twenty-seven months before these new abdominal symptoms, the patient was found to have a spiculated suprahilar 4.5 × 2.6 cm right upper lobe (RUL) nodule on a screening low-dose CT scan and multiple sub-centimeter left lung nodules consistent with lung-RADS 4X. A positron emission tomography/CT (PET/CT) scan showed augmented activity in the RUL mass. Bronchoscopy-attained tissue sample showed that the RUL mass was a NSCLC, consistent with adenocarcinoma (Fig. 1a–c). Lymph node sampling was negative for nodal involvement, consistent with stage IIIA lung adenocarcinoma (T4N0M0). Program death ligand-1 expression was 15% (April 2020). Surgical resection of the mass was planned but aborted at the time of surgery due to findings of encasement of the pulmonary artery and superior vena cava. The patient subsequently completed 7 rounds of carboplatin and paclitaxel and 8 rounds of radiation therapy (July-September 2020). On follow-up, a repeat CT scan revealed a decrease in the RUL mass from 4.5 × 2.6 cm to 3.5 × 2.1 cm (November 2020). Adjuvant immunotherapy with durvalumab was subsequently started and 3 rounds were received (December 2020 – January 2021) before premature discontinuation due to pneumonitis. A steroid taper was prescribed and completed for this pneumonitis. Staging chest CT showed an increase in the RUL mass to 5.0 × 2.8 cm (December 2020), and a further follow-up chest CT showed an increase in the RUL mass to 6.5 × 2.2 cm (June 2021) without distant metastasis. In the interim between June 2021 and August 2022, the patient was followed routinely by the pulmonary medicine clinic for respiratory symptom management, radiation oncology clinic, and the hematology-oncology clinic. She underwent a single thoracic, abdominal, and pelvic CT scan in September 2021, which showed no distant metastasis and relatively stable lung nodules. The

patient further had 5 subsequent chest CT scans, with the last in June 2022. These CT scans showed stable appearance of the lung nodules and post-radiation changes consistent with radiation fibrosis.

The patient presented to her primary care physician in July 2022 with complaints of epigastric pain associated with constipation, loss of appetite, and weight loss. Symptoms had been ongoing for a few months. An abdominal and pelvic CT scan showed a mass in the head of the pancreas that measured 3.1 × 3.4 cm and pancreatic ductal dilatation to 7 mm. The patient was immediately referred to the oncology clinic. At the oncology clinic, she was referred to gastroenterology for endoscopic ultra-sound-guided biopsy of the pancreatic head mass (August 2022).

The pathology of the pancreatic mass showed tumor cells with nuclear pleomorphism, prominent nucleoli, irregular nuclear contours, and coarse chromatin. Tumor cells showed CK7, TTF-1, and Napsin-A positivity on immunohistochemical staining, a pattern consistent with pulmonary origin (Fig. 1d–f). Tumor cells were negative for CDX-2, KOC, and synaptophysin. An immunostain for Smad-4 showed a mixed staining pattern. Furthermore, when the tumor cells of the pancreatic lesion were compared to those of the patient's original lung adenocarcinoma, they were found to be morphologically similar. Overall, the cytomorphology and immunoprofile support the finding of a lung adenocarcinoma metastasized to the pancreas (Fig. 1).

At the time of the endoscopy (August 2022), all liver enzymes were within normal limits: AST 35 U/L (normal 4–35 U/L), ALT 23 U/L (normal 10–35 U/L), ALP 74 U/L (normal 35–130 U/L). Total bilirubin was also within normal limits: 0.5 mg/dL (normal <1.2 mg/dL), as was direct bilirubin: 0.2 mg/dL (normal <0.3 mg/dL); a lipase level was not sent. CA 19.9 was 22.5 U/mL (normal <35 U/mL). A PET/CT scan was performed and showed fluorodeoxyglucose-avid mass in the pancreatic head with an SUV max of 13.3 and increased uptake in the porta hepatis with an SUV max of 4.2; however, no other regions of metastases were appreciated, and no lymphadenopathy was noted (September 2022) (Fig. 2–4a,b). A brain MRI scan was negative for intracranial metastasis (September 2022).

Our patient was a poor surgical candidate and underwent palliative radiation therapy to the pancreatic mass, with subsequent combination chemotherapy with carboplatin and pemetrexed, initiated in November 2022. Three cycles were completed by December 2022. Chemotherapy was subsequently held when the patient was admitted in December 2022 for generalized weakness and dyspnea at rest. The patient was found to have electrolyte derangements and an acute anemia with a hemoglobin nadir of 6.9 g/dL, requiring transfusion. A CT scan of the chest revealed a new 9 mm left lower lobe nodule during this admission. The patient was discharged home in January 2023. A staging PET/CT scan was performed in February 2023 which showed decreased metabolic activity in the pancreatic mass, and metabolic activity in the new left lower lobe nodule. At this point in February 2023, the patient expressed uncertainty regarding treatment continuation during a visit with her oncologist, as she felt too fatigued. No further treatments were given after the third cycle in December 2022.

While visiting the pulmonology clinic in March 2023, a rapid response was called when the patient was noted to be saturating at 87% on 3 L of oxygen via nasal cannula, despite not requiring baseline oxygen supplementation. She was also noted to be using her accessory muscles, with a blood pressure of 84/70, and heart rate of 138. The patient reported increased dyspnea, cough, and generalized weakness. The patient was taken to the emergency department and subsequently admitted to the hospital. Imaging studies on admission revealed right lung consolidation concerning for an infectious process, with an associated loculated pleural effusion. The patient was initiated on treatment for acute hypoxic respiratory failure in the context of sepsis secondary to pneumonia. Broad-spectrum antibiotics including vancomycin, azithromycin, and cefepime were initiated. Additionally, oxygen supplementation

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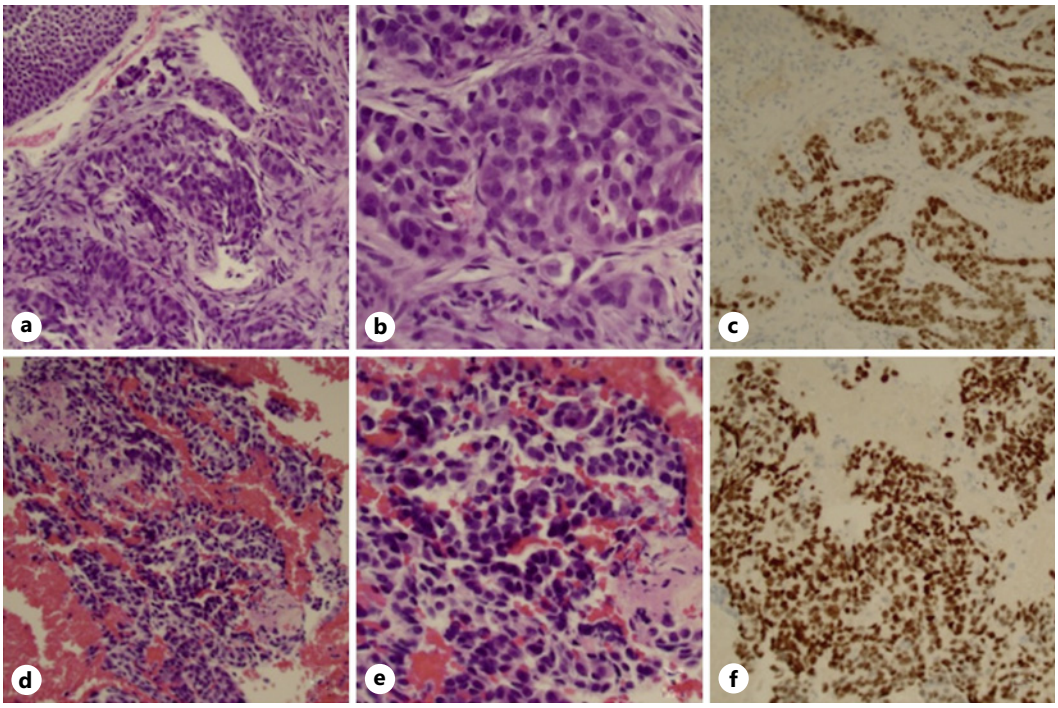

Fig. 1. a–c Right upper lobe endobronchial lesion biopsy. Infiltrating glandular epithelial cells are noted below bronchial type mucosa. The tumor cells show nuclear pleomorphism, prominent nucleoli, irregular nuclear contours, and coarse chromatin. Mitotic figures and apoptotic cells are readily seen. H&E ×20 (**a**); H&E ×40 (**b**); the tumor cells are positive for a TTF-1 immunostain. TTF-1 ×20 (**c**). **d–e** Pancreatic head mass fine needle aspiration biopsy. Pleomorphic glandular epithelial cells are noted on the cellblock material. The tumor cells show prominent nucleoli, irregular nuclear contours, and coarse chromatin. H&E ×20 (**d**); H&E ×40 (**e**); the tumor cells are positive for a TTF-1 immunostain. TTF-1 ×20 (**f**).

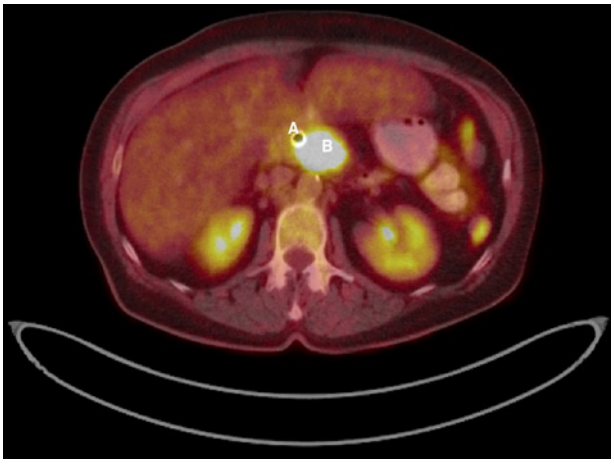

Fig. 2. PET/CT scan. Stented common bile duct (A). FDG-avid pancreatic head mass (B). FDG, fluorodeoxyglucose.

was initiated using bilevel-positive airway pressure. On the sixth day of admission, the patient experienced an episode of altered mentation and worsening hypoxemia which necessitated a critical care consult. The patient required vasopressor support and continued bilevel-positive airway pressure at this point. The palliative medicine team was consulted and engaged in a

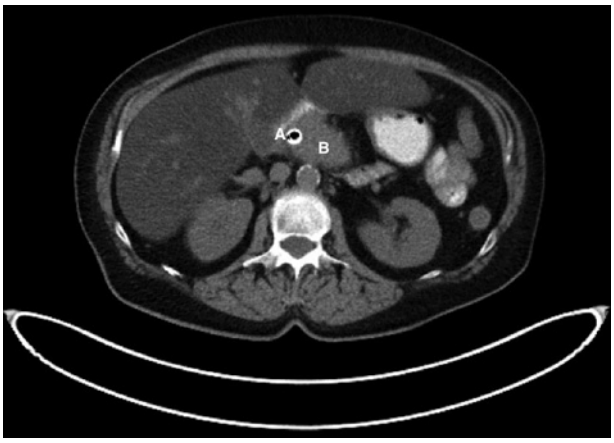

Fig. 3. CT scan showing pancreatic mass. Stented common bile duct (A). Pancreatic head mass (B).

discussion with the patient's family regarding the transition to inpatient hospice care. Subsequently, this transition was implemented on the eighth day of the patient's admission in March 2023. The patient subsequently passed peacefully under comfort measures on the eighth day of admission (Fig. 5). The CARE Checklist has been completed by the authors and has been attached as a online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531841).

Discussion

Pancreatic metastasis from lung cancer is rare. A single-center study by Yoon et al. [14] attributes 10% of isolated pancreatic metastasis to primary lung tumors, while renal cell cancers made up the largest contributors. Isolated pancreatic metastasis from lung cancers is noted in literature to occur in the range of 5–11% [15, 16]. Small cell lung cancer (SCLC) is most frequently associated with pancreatic metastasis compared with other histological subtypes of lung cancer [17, 18]. Postmortem studies by Jereczek et al. [19] showed that pancreatic metastasis of SCLC occurs in 12% of SCLC patients. Other histological subtypes of lung cancer appear to be more rarely associated with isolated pancreatic metastasis. The rarest histological subtype associated with metastasis to the lungs is squamous cell carcinoma (1.1%), followed by large cell (1.9%), and adenocarcinomas (2.4%) [12, 20]. Isolated pancreatic metastasis has been noted to be a silent disease in up to 50% of patients, with symptoms, if present being non-specific. Only a few patients have isolated pancreatic metastatic lesions that result in obstructive symptoms [21], and pancreatitis is a rare manifestation [22].

We reviewed the literature for cases specifically concerning isolated pancreatic metastasis from lung primaries; most cases appear to be metachronous. There was a latency of over 2 years (27 months) in our patient between the initial lung cancer diagnosis and the discovery of an isolated pancreatic metastatic lesion. In the literature reviewed, the median latency between the primary lung cancer and isolated pancreatic metastasis was 20 months (IQR 56 months); average 21.9 months (SD: 20.1) (Table 1).

The prognosis of isolated pancreatic metastasis from lung primaries is unclear but some studies suggest a poor prognosis, with a median survival of 5.5 months in one study; however, this study did not focus on isolated pancreatic metastasis, as cases with extra-pancreatic metastases were included [30]. Another study likewise shows a poor prognosis following metastasectomy in isolated metastasis to the pancreas, with a median survival of 5 months [30]. Reddy et al. [31] report a similar poor prognosis with a median survival of 6 months in

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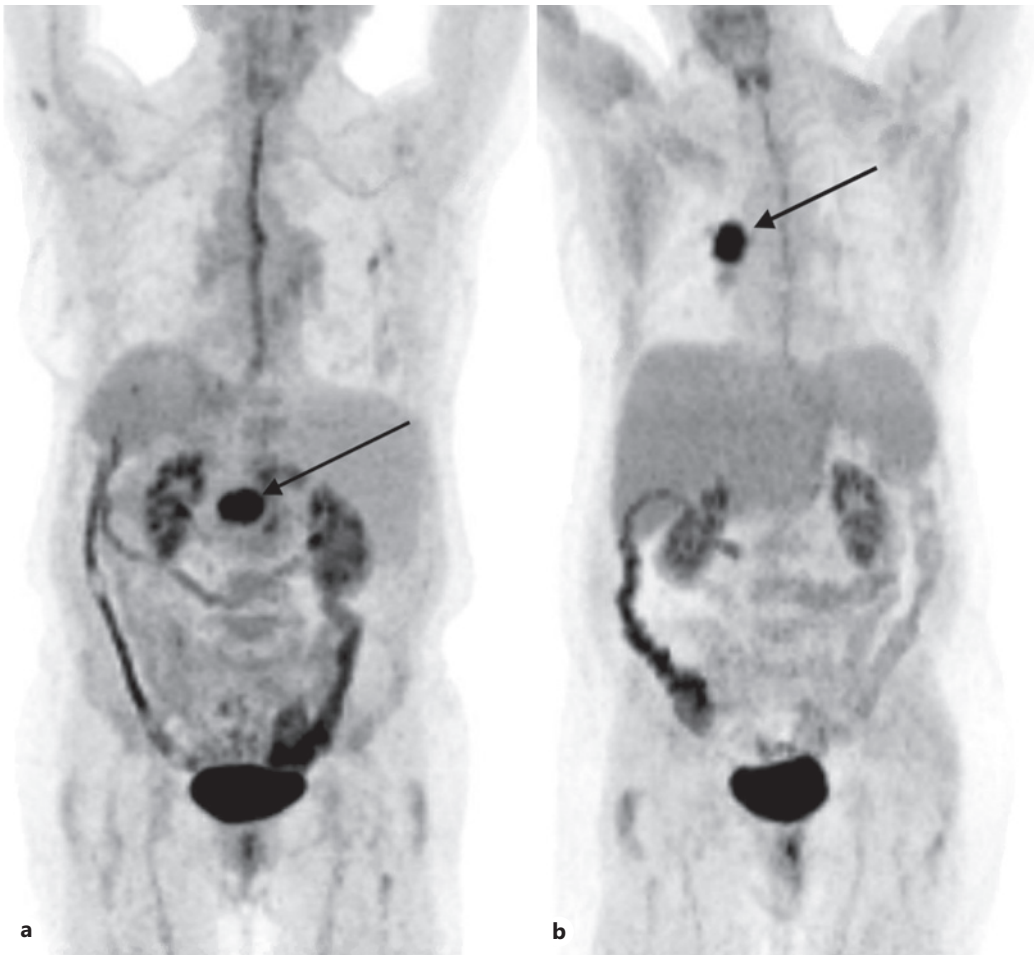

Fig. 4. a MIP image showing FDG-avid pancreatic head mass and no lung mass in September 2022. **b** MIP image showing FDG-avid lung mass and no abdominal masses in April 2020. FDG, fluorodeoxyglucose.

patients with pancreatic metastasis from lung primaries; this study also does not specifically highlight isolated pancreatic metastasis, and survival may be better in patients with isolated metastasis from lung primaries. It is likely that the prognosis of isolated pancreatic metastasis from the lung will be similar to the prognosis associated with the primary lung tumor [23].

The best approach to treatment of isolated metastasis from lung primaries to the pancreas is currently uncertain. Several studies have shown good success with surgical resection [24, 31, 32]; other studies have shown an association between pancreatic metastasectomy and severe morbidity [21]. Nonetheless, in good surgical candidates, an acceptable approach to treatment may be a combination of surgical and medical interventions, while poor surgical candidates may be limited to palliative radiation therapy and chemotherapy, and in the event of biliary obstruction, palliative stenting of the biliary tract. Perfetti et al. [25] did show complete resolution of pancreatic metastasis with a chemotherapy-only approach, while other studies have not shown similar outcomes [26–29]. In patients who are appropriate for surgery, it is unknown if the combination of surgery and chemotherapy provides any benefit over chemotherapy alone.

Isolated pancreatic metastasis is a very rare manifestation of primary lung cancer reported to be associated with poor outcomes. Our patient survived 7 months from the initial diagnosis of the isolated pancreatic lesion, despite completing palliative radiation therapy and

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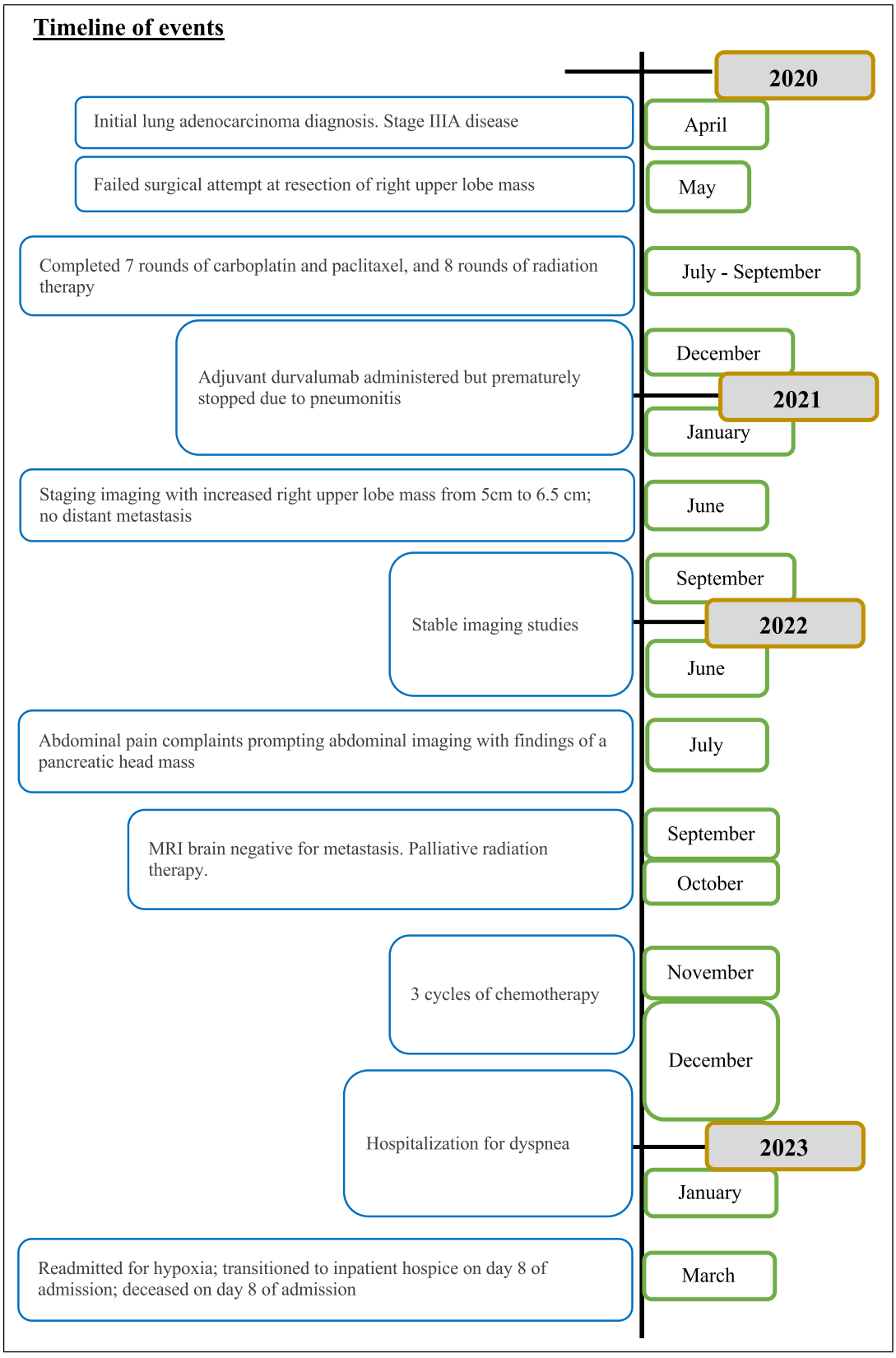

Fig. 5. Timeline of case.

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Table 1. Literature review of isolated pancreatic metastasis from primary lung cancer

Reference	Sex	Age	Primary tumor laterality	Largest diameter	Tumor histology	Primary tumor stage	Time-to-isolated pancreatic metastasis, months	Location on pancreas	Survival, months
Seki et al. [20] 1998	F	62	Left	30 mm	Poorly differentiated adenocarcinoma	IIIB	55	Body	29
Moazzam et al. [23] 2002	M	54	Right	INA	Squamous cell carcinoma	INA	Synchronous diagnosis	Head	INA
Pericleous et al. [24] 2008	M	56	Right	30 mm	Adenocarcinoma	INA	Synchronous diagnosis	Head	>18 *
Perfetti et al. [25] 2008	M	66	INA	INA	Adenocarcinoma	INA	24	Head	>6 *
Mori et al. [26] 2008	M	56	Right	75 mm	Adenocarcinoma	IIIB	22	Head	INA
Jeong et al. [27] 2006	F	65	Left	INA	Small cell carcinoma	INA	Synchronous diagnosis	Head and tail	>11 *
Igai et al. [28] 2014	M	67	Right	25 mm	Adenocarcinoma	IIA	60	Head	>6 *
Z'graggen [29] 1998	INA	INA	INA	INA	INA	INA	16	Head	34
	INA	INA	INA	INA	INA	INA	18	Head	18
	INA	INA	INA	INA	INA	INA	24	Uncinate process	12

F, female; M, male; INA, information not available. *Months after diagnosis of isolated pancreatic metastasis.

being started on chemotherapy that was prematurely aborted. Survival in our patient aligns with current reports of poor survival. The best approach to management of this unusual presentation remains unknown.

Acknowledgment

We thank Dr. Phillips Shibu (Department of Diagnostic Radiology, Geisinger Wyoming Valley Hospital) for providing guidance on image interpretation.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. All procedures described here were performed in accordance with the ethical standards of the Institutional Research Committee and with the Helsinki Declaration (as revised in 2013). No approval was required by the institutional review board of Geisinger Health System, Wilkes Barre, PA, USA, for the preparation of this case report manuscript per institutional policies, with the requirement of complete anonymity of the patient and complete de-identification of any patient data published in association with this case report. Prior to the patient's death, written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funds were received for the preparation of this manuscript.

Author Contributions

O.A. was responsible for design, literature review, and manuscript writing. M.P. was responsible for manuscript writing. A.A. was responsible for conception and manuscript writing. All authors were responsible for the final approval of the version to be published.

Data Availability Statement

All relevant data relating to this case report has been provided. Any other data that have not been provided is identifiable patient information which is only available to institutional personnel with access to the institution's electronic medical record system and with appropriate authority to access these records. Further inquiries can be directed to the corresponding author.

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