Case study

Stage IV non-small cell lung adenocarcinoma in complete response for 5 years post-first-line Nivolumab immunotherapy: Are we talking about a cure?

Abstract

Background: Metastasis of the central nervous system (CNS) is one of the frequently occurring complications of advanced non-small cell lung cancer (NSCLC) and has been observed in 24–44% of patients. Patients suffering from NSCLC along with CNS metastases have a generally poor prognosis.

Case Report: A 57-year-old nonalcoholic, non-diabetic, heavy smoker male patient was diagnosed with stage IV NSCLC *(*non-small cell lung cancer) (Adenocarcinoma), PD-L1 expression 80% with liver, spleen, and brain metastases. In June 2016, the patient was diagnosed with Stage III-A EGFR wild right-sided lung adenocarcinoma (T4N0M0), for which he underwent Curative Concurrent chemo-radiotherapy in Jordan, followed by two cycles of Etoposide plus CDDP (Cisplatin). In February 2017, the patient came to the hospital with the chief complaint of excessive hemoptysis. His CT scan showed an appearance in keeping with the right upper-lobe cavitating tumor with possible contralateral lung, splenic, and hepatic metastases. The patient was offered pneumonectomy but refused it. Interventional radiology (IR) tumor embolization of the apical and posterior (A1 and A2) branches of the right superior pulmonary artery with no procedural complication was performed to stop the bleeding.

At the end of that same month, on February 28, 2017, he presented to emergency with seizures, for which a contrast CT scan showed two enhancing lesions, one of the left parietal lobe posteriorly 1.8 cm with marked white matter oedema causing a mass effect and the effacement of the posterior horn of the left lateral ventricle. The second is a small ring-enhancing deposit of the right occipital lobe 6 mm with surrounding oedema.

The liver biopsy failed to show any malignancy. After the MDT discussion, the largest lesion in the brain was removed and a small lesion was kept. The left occipital metastasis was resected and was found to be a metastatic adenocarcinoma of lung origin. It was positive for TTF-1 and

positive for Moc 31. P63 and CK5/6 were negative (no squamous component is seen). No brain radiotherapy was offered. First-line palliative Nivolumab was started on March 20, 2017. Nivolumab first proved to be highly successful against brain metastases. However, it was discontinued as the patient developed myelitis after seven months of continuous treatment. After the discontinuation and improvement of myelitis symptoms, Nivolumab was resumed. The amazing thing about this treatment approach was that his disease was completely cleared up and he had been in complete remission for five years. Additionally, all of his tumor indicators had decreased and normalized.

Conclusion: Our case report demonstrated a full response to first-line Nivolumab in a patient with PD-L1-positive NSCLC having visceral and brain metastases. However, our patient suffered from myelitis, which may have been a Nivolumab-related adverse event.

The important point is that he has been achieving a durable complete response for nearly 5 years, so are we talking about the certain biology of a tumor that can be cured by immunotherapy?

Keywords: Brain metastases, Nivolumab, non-small-cell lung cancer, lung cancer, PD-L1

Introduction

The brain is one of the most common sites of lung cancer metastasis. According to recent reports, the prevalence of lung cancer metastases in the brain has increased in previous years, as approximately 50 percent of non-small cell lung cancer (NSCLC) patients develop brain metastases(1). The prognosis is poor for patients with CNS metastases(2). Although local interventions, such as radiotherapy and surgery, have been added to standard care, the therapeutic efficacy of chemotherapy is still restricted due to the presence of the blood-brain barrier(3). However, the new generation of ALK inhibitors and EGFR, such as alectinib and osimertinib, have demonstrated remarkable activity in NSCLC patients with brain metastases and may alter their future therapy (4).

Nivolumab is a human immunoglobulin G4 anti-programmed cell death 1 (PD1) antibody that has been recommended as a second-line monotherapy for the treatment of advanced NSCLC. According to clinical research, in phase III trials, Nivolumab increased both the overall survival rate and progression-free survival (PFS) compared to docetaxel in patients with locally advanced NSCLC with progression following first-line treatment. In these studies, individuals with unstable or untreated brain metastases were omitted, and the maximum corticosteroid dose tolerated (10 mg per day of prednisone) was given within the previous two weeks. Additionally, Nivolumab's effectiveness seems to be dependent on the presence of PD-L1 expression on tumor cells(5). However, studies are limited regarding the efficacy of Nivolumab against CNS metastases, particularly in patients with positive PD-L1 expression. In this study, we discuss the case of a patient presented with non-squamous lung carcinoma who received Nivolumab as first-line treatment (the only immunotherapy approved for lung cancer in 2017) for visceral (liver and spleen) and symptomatic brain metastases.

Case Report

In 2017, a 57-year-old nonalcoholic, non-diabetic, heavy-smoking male patient was diagnosed with stage IV non-small cell lung cancer PD-L1 positive, 80% expression with liver, spleen, and brain metastases. In June 2016, the patient was admitted to the hospital with a major complaint of hemoptysis. The positron emission tomography revealed a mass of about 7.5 cm in his right lung. Tumor staging (T4 N0 M0) was initially confirmed. A biopsy was performed and a pathology profile revealed adenocarcinoma, EGFR wild type. Additionally, the PDL 1 staining performed by the Mayo Clinic showed 80% of positive tumor cells. At that time, the patient was diagnosed with Stage III-A lung adenocarcinoma. After the confirmation of his diagnosis, he was treated at Jordan Hospital and received Concurrent chemotherapy and radiotherapy, followed by two cycles of Etoposide + CDDP (Cisplatin).

After completion of the chemotherapy and radiotherapy course, a CT scan was performed and indicated a high suspicion of liver and spleen metastases, and right hilar mass. Later, in February 2017, the patient presented to the hospital complaining of a large amount of hemoptysis. At that time, it was suggested that his hemoptysis could be due to the presence of a tumor invading the right bronchial tree and secondary liver and spleen metastases. However, the patient was treated conservatively with embolization of the tumor.

Moreover, on February 26, 2017, a biopsy was performed to evaluate liver lesions, and the pathology profile appeared to be negative for malignancy. Furthermore, on February 28, 2017, the patient was admitted to the emergency department with complaints of dizziness, seizures, and loss of consciousness. Computerized tomography of the brain with IV contrast showed a left parietal brain mass measuring 1.8 cm with marked edema and a 6-mm occipital mass. The

patient was assessed by a neurologist and his seizures were controlled using Phenytoin and Alprazolam. Later, he underwent a left side craniotomy and a tumor resection was performed. After the complete resection of the tumor, pathological tests were conducted to look out for other pathologies. The pathology profile revealed TTF1 positive metastatic primary lung. For the treatment of metastatic lung, the patient received a steroid tapering dose without any additional radiotherapy. Additionally, on March 20, 2017, the patient started to receive Nivolumab immunotherapy. On June 12, 2017, after two months under Nivolumab, a CT brain was conducted. The findings revealed no signs of metastases or abnormal enhancement. Moreover, on the same day, a CT scan of the neck, chest, abdomen, and pelvis was performed and showed improvements in the right cavitating lung mass, along with the resolution of the nodular opacities of both lungs, as well as improvements and the reduction in the size of the liver and splenic lesions. No additional new metastases were reported.

On August 3, 2017, an ultrasound of his abdomen was performed and showed a mildly enlarged, homogenous liver of about 18 cm. No focal lesion could be identified on this examination, and no dilatation of intrahepatic biliary radicles was noted. The pancreas, portal vein, gallbladder, CBD, and left kidney were found to look normal. However, the right kidney showed a cortical cyst measuring 2.32 cm, and the spleen showed a small ill-defined solid lesion measuring 1.2 x 1.24 cm. Moreover, no evidence of ascites was found.

Furthermore, on September 16, 2017, the patient underwent an MRI of the brain. The findings revealed no significant interval changes. In the next following month, on September 24, 2017, the patient underwent a CT scan of his chest, abdomen, and pelvis that showed a further reduction in the size of the liver and splenic lesions, indicating that the patient was positively responding to the Nivolumab immunotherapy.

Later, on October 7, 2017, the patient underwent MRI thoracolumbar spine. The findings revealed superior endplate fractures of the D4 to D7 levels, diffuse T2 hyperintensity involving the thoracic cord, which most likely represents immune-related myelitis, and the absence of vertebral metastatic lesions throughout the thoracic and lumbar spine. On October 28, 2017, another MRI test was performed. The findings revealed no significant changes. The case was discussed with a multidisciplinary team. Some doctors advised putting Nivolumab on hold due to possible myelitis, secondary to Nivolumab. Other doctors were advised to continuously monitor the patient's condition. On November 17, 2017, another MRI test was performed. The findings revealed the clear autoimmune possibility of myelitis. The MDT team agreed to stop Nivolumab therapy. Nivolumab was stopped on October 10, 2017.

Again, on November 28, 2017, the patient underwent a CT scan (neck, chest, abdomen, and pelvis). The results indicated no evidence of the disease's progression and the resolution of previously noted liver and splenic lesions. These changes indicated that the patient was responding positively to the treatment approach. The MRI brain scan reported no marked changes. Nivolumab therapy was resumed on January 4, 2018.

Later, on January 17, 2018, the patient was advised to undergo an MRI if his symptoms persisted to rule out bone marrow metastases. Additionally, on February 7, 2018, the patient underwent a CT brain scan. The report indicated no signs of space-occupying lesions or abnormal enhancement, previous left-sided parietal occipital craniectomy with post-operative parenchymal gliosis, normal basal cisterns, and ventricles, and no bony metastasis. A CT scan of his chest, abdomen, and pelvis reports also indicated no evidence of the disease's progression.

Later, on February 27, 2018, an MRI of his spine revealed the same findings, along with the complete regression of the previous spinal cord seen from C5, down the lower spinal cord

region, and hyperintensity on T2 and STIR sequences. Additionally, no vertebral metastatic lesions were seen throughout the cervical, thoracic, and lumbar spine, except in the superior endplate fractures of D4 to D7 levels due to the changes in radiotherapy.

Additionally, on July 10, 2018, the positron emission tomography revealed scarring fibrosis and traction bronchiectasis in the right midzone. Moreover, there were no notable focal soft tissue nodules or hypermetabolic uptake to suggest any residual or recurrent disease.

The patient received Nivolumab therapy continuously for two years. Later, on July 7, 2019, a CT scan reported no evident distant metastasis. Other findings were unremarkable. However, the prostate was mildly enlarged with a transverse diameter estimated at 4.7 cm. At the end of that month, a CT scan of his head/brain showed stable appearances of the postsurgical changes in the left posterior parietal lobe with no marked evidence of a metastatic deposit.

Furthermore, a CT scan of the brain, chest, abdomen, and pelvis performed in November 2020 did not show any metastasis or progressive disease. The patient was also examined and assessed. He seemed to be vitally stable but complained about numbness and other symptoms of neuropathy. Additionally, there were no further complaints of dizziness or other symptoms except that the patient developed dysuria.

Moreover, CEA (carcinoembryonic antigen) levels were found to be decreased by 1.87 mcg/L and (prostate-specific antigens) PSA levels were 4.26 mcg/L, respectively. After a year, in July 2021, the patient contracted Covid-19, but it was later resolved. Furthermore, on July 28, 2021, a CT of his head/brain showed evidence of previous left posterior parietal craniotomy and stable underlying hypodense area of gliosis/encephalomalacia in the left posterior parietal lobe. Grey-white matter differentiation appeared to be preserved in the rest of the bilateral cerebral

hemispheres. Additionally, there was no other sign of obvious focal lesions, and no hydrocephalus or midline shift was noted. The brain stem and cerebellum showed no gross abnormality. No unusual intraparenchymal enhancement on post-contrast images was seen either, and both orbit sinuses appeared clear. On dedicated bone window images, no definite lytic or sclerotic bone lesions were noted.

Similarly, on July 28, 2021, CT scan findings revealed stable appearances with no evidence of disease recurrence or new metastasis. As expected, the outcomes were favorable, resulting in significant improvements in the patient's symptoms and overall condition. All tumor markers decreased again and normalized, and the patient was reassured. The patient's follow-up plan included PET scan testing, an MRI of the brain for reevaluation, and blood testing until the next visit. The referral was made to the urology clinic and to the gastroenterology department for upper and lower endoscopy as the patient had difficulty swallowing solids and liquids with chronic constipation for a month. The patient was also referred to the neurology department for chronic peripheral extremity numbness, to the physiotherapy department for lower extremity weakness, and to the pain management team to manage his chronic pain syndrome.

Lastly, on July 22, 2022, a PET scan and MRI of the brain were performed and indicated no marked evidence of FDG avid residual or metastatic disease. However, the suggestion of ongoing gastritis is clinically correlated; an upper endoscopy might be recommended if clinically warranted.

Discussion

In this study, we present the case of a patient with stage IV non-small cell lung cancer, PD-L1 positive 80% expression with liver, spleen, and brain metastases. Studies have indicated that PD-L1 expression is a prognostic biomarker for anti-PD-1 therapy(6). Additionally, it has been observed that smoking can cause lung epithelial cells to express PD-L1, and smokers exhibit higher levels of PD-L1 expression than non-smokers(7). For example, in a recent study, the percentages of PD-L1 patients with NSCLC were 19%, 12.8%, and 7.3% in never smokers, former smokers, and current smokers, respectively(8). In addition, we were unable to investigate the PD-L1 expression of brain metastasis in our patient. The brain metastasis likely expressed PD-L1 at the same or a higher level than the initial lesion, resulting in a favorable therapeutic response.

Nivolumab is one of the PD-1 inhibitor drugs. It was the first PD-1 pathway-blocking medication to enter clinical development, beginning in 2006 with a first-in-human experiment(9). Since then, the use of anti–PD-L1 medicines has been extended to multiple tumor indications, firmly establishing PD-1 as a clinically recognized cancer therapeutic target(10). Nivolumab, a completely humanized IgG4 anti-PD-1 antibody, has been indicated for the treatment of patients with advanced or metastatic NSCLC and brain metastasis (10). However, the mechanism by which PD-1 inhibitors suppress brain metastases remains unknown(11). According to preclinical studies, Nivolumab stimulates T-cell trafficking across the blood-brain barrier without directly acting on the tumor(3). This indicated that Nivolumab was successful against brain metastases.

Additionally, in our report, Nivolumab was suggested for both NSCLC and brain metastases. Even though the patient responded favorably to Nivolumab therapy after seven months of treatment, the chemotherapy was discontinued when the patient started experiencing serious

neurological symptoms. In the majority of the circumstances, the worsening of neurological symptoms suggests the advancement of brain lesions(12). But, in our case, the MRI reports revealed no significant changes related to a brain tumor as no vertebral metastatic lesions throughout the cervical, thoracic, and lumbar spine were noted in the MRI scan. However, the superior endplate fractures of D4 to D7 levels and previous left-sided parietal occipital craniectomy with post-operative parenchymal gliosis were observed on the MRI scan. There was also diffuse T2 hyperintensity involving the thoracic cord which most likely represents autoimmune myelitis, indicating that the neurological symptoms are possible secondary to Nivolumab.

Our report indicated that immunotherapy was still effective in controlling the patient's visceral and brain metastatic lesions, which was consistent with prior research(13), given that the neurological symptoms could be subsequent to Nivolumab. Moreover, it tells us that neurological symptoms may not reflect the genuine disease state of immunotherapy patients and that the actual condition of the brain tumor may directly influence the treatment plan. Therefore, it is vital to be more cautious when evaluating the success of immunotherapy in patients with brain metastasis, which will help distinguish between symptoms produced by the tumor’s progression and immunotherapy’s side effects.

Furthermore, compared to cytotoxic chemotherapy, Nivolumab induced a long-lasting response that remained even after the treatment’s cessation. According to aggregated efficacy and safety data from the phase III “CheckMate017” and “CheckMate057” trials, the 5-year survival rate was 13.4%. (14) Our patient's response was stable and durable, lasting five years and still counting.

Conclusion

Metastasis of the central nervous system (CNS) is one of the frequent complications of advanced non-small-cell lung cancer (NSCLC). Patients with CNS metastases have a poor prognosis. The standard treatment for stage IV lung cancer with a satisfactory performance status is palliative chemotherapy, immunotherapy, or targeted therapy depending on the molecular driver. Our case study illustrates a complete response to Nivolumab in patients with PD-L1-positive NSCLC with visceral and brain metastases. However, our patient suffered from myelitis, which may have been a Nivolumab-related adverse event. Therefore, it is vital to be more cautious when evaluating the success of immunotherapy in patients with brain metastasis as it will help distinguish between symptoms produced by the tumor's progression and immunotherapy's side effects. Indeed, while most patients tolerate the treatment quite well, some develop autoimmune side effects. This occurs when the stimulation of their immune system results in an immune attack on their normal tissues. Such toxicities might affect almost every organ in the body and occur at any point during the treatment. Despite these risks, immune checkpoint inhibitors represent one of the most promising advances in cancer treatment in the past 50 years.

Of note, Nivolumab is FDA-approved for the second-line treatment of non-small cell lung cancer. We must take into consideration the fact that Nivolumab was the only available immunotherapy in 2017 and an acceptable option for the first line at that time. For this reason, the drug was used.

To better predict the success of Nivolumab, additional research is required to better comprehend its mechanism and identify biomarkers that could better predict its efficacy. Though immunotherapy is among the past decade's biggest breakthroughs in medical lung cancer treatment, doctors and patients alike need to have frank conversations about the capabilities

of immunotherapy and understand that while it allows us to extend the lives of patients with metastatic lung cancer, it's not usually curative. As doctors and researchers, curing this difficult disease is our long-term goal, but we still have a lot more work to do to make that a reality for most patients.

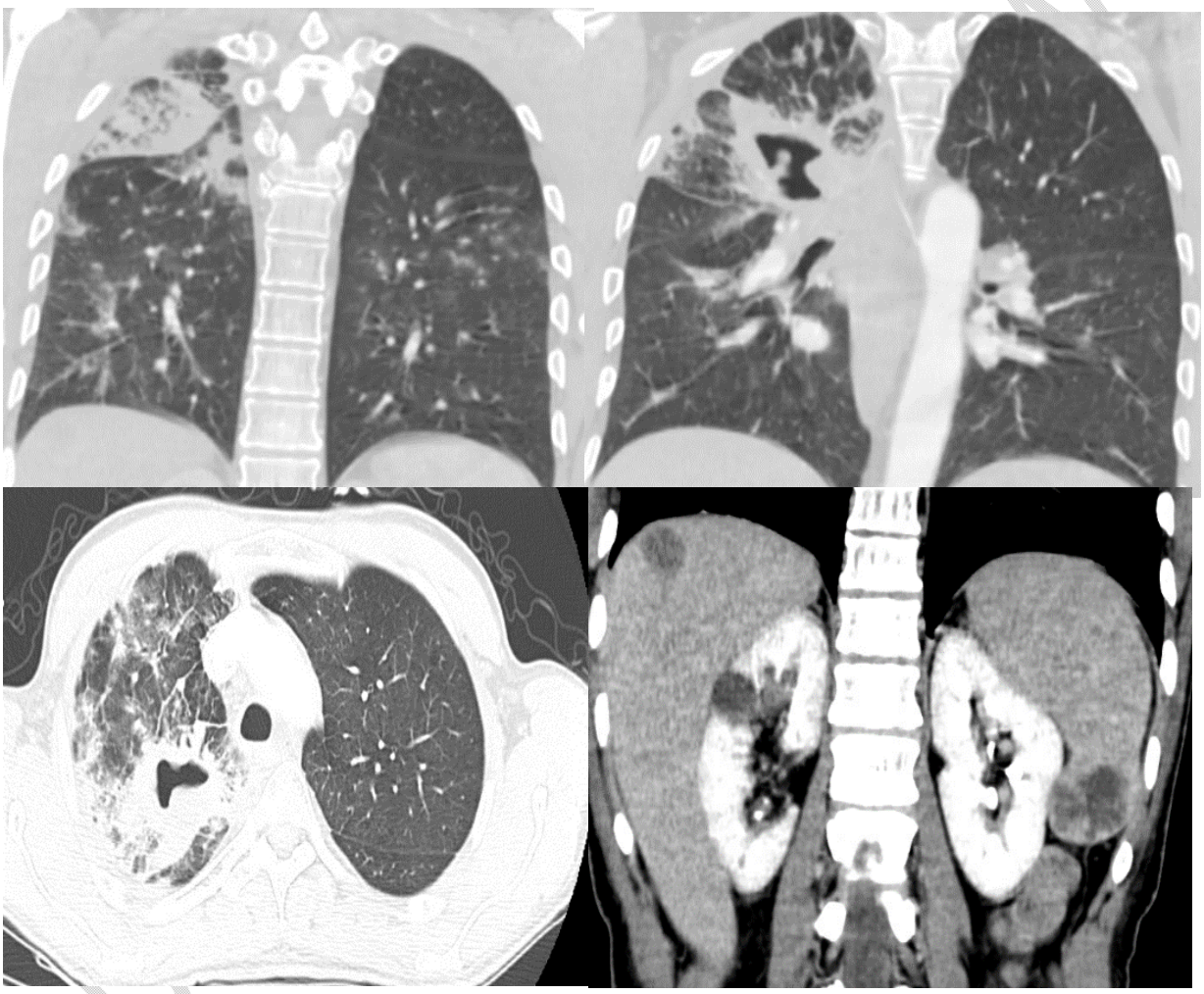

Figure 1: CT scan at presentation

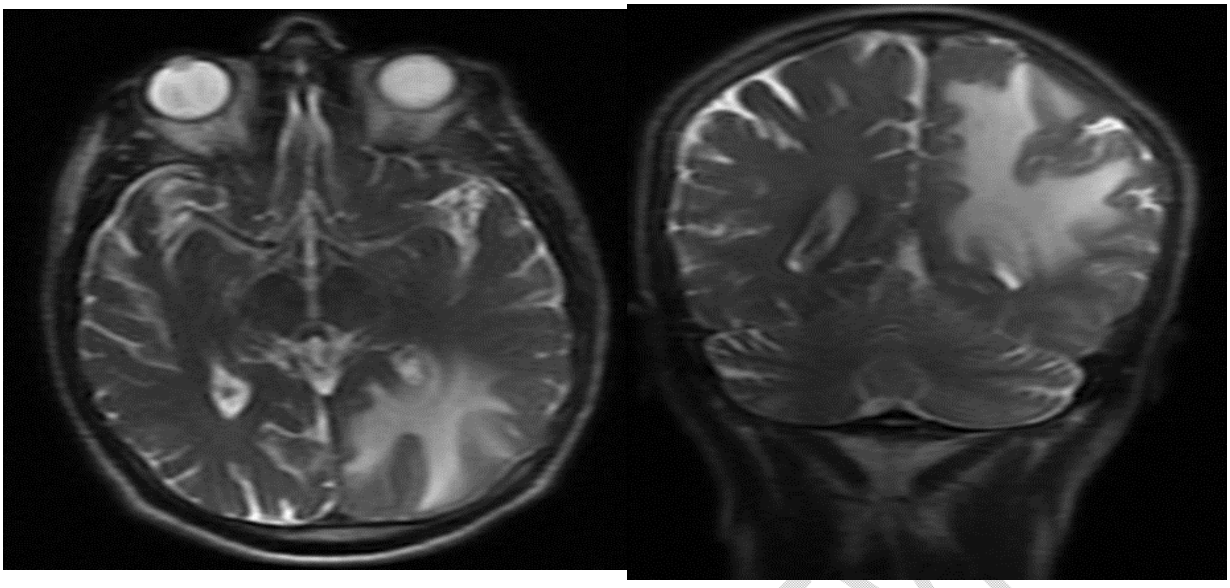

Figure 2: MRI of the brain

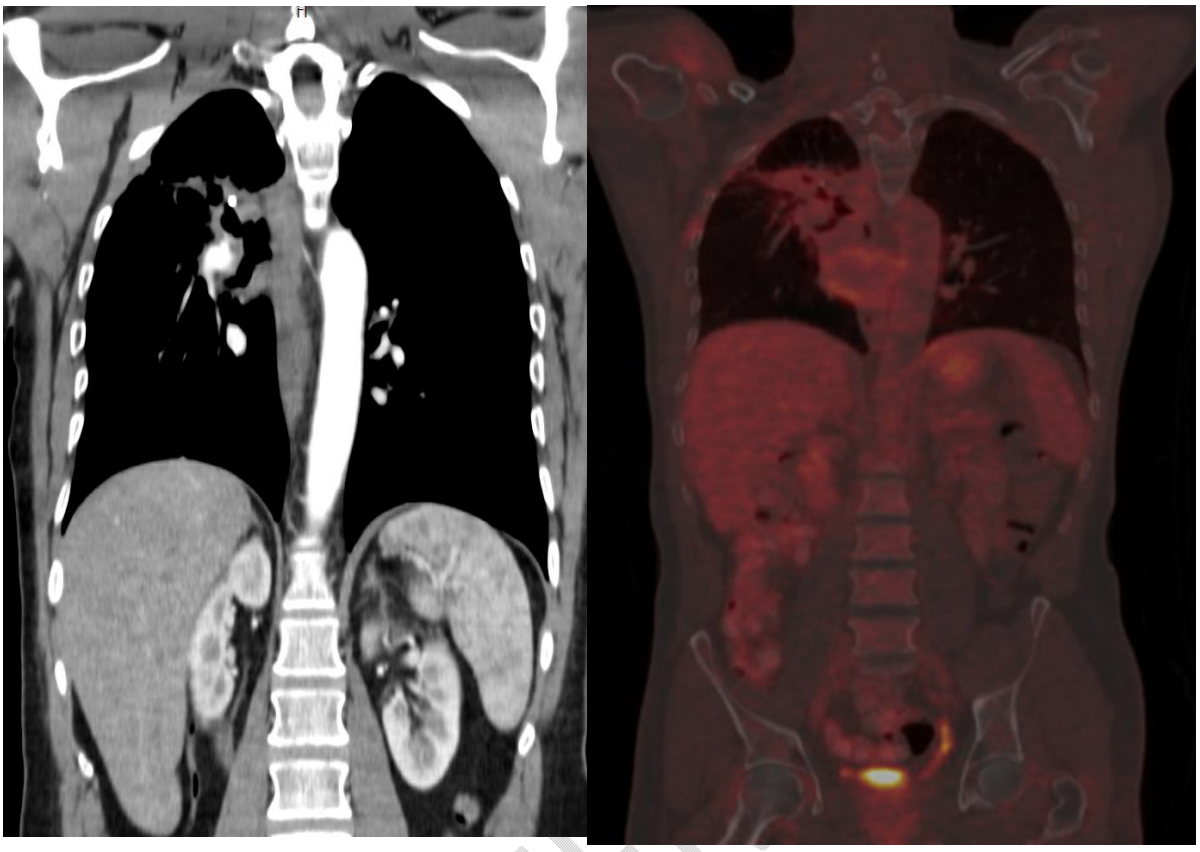

Figure 3: PET and CT scan conducted in 2018

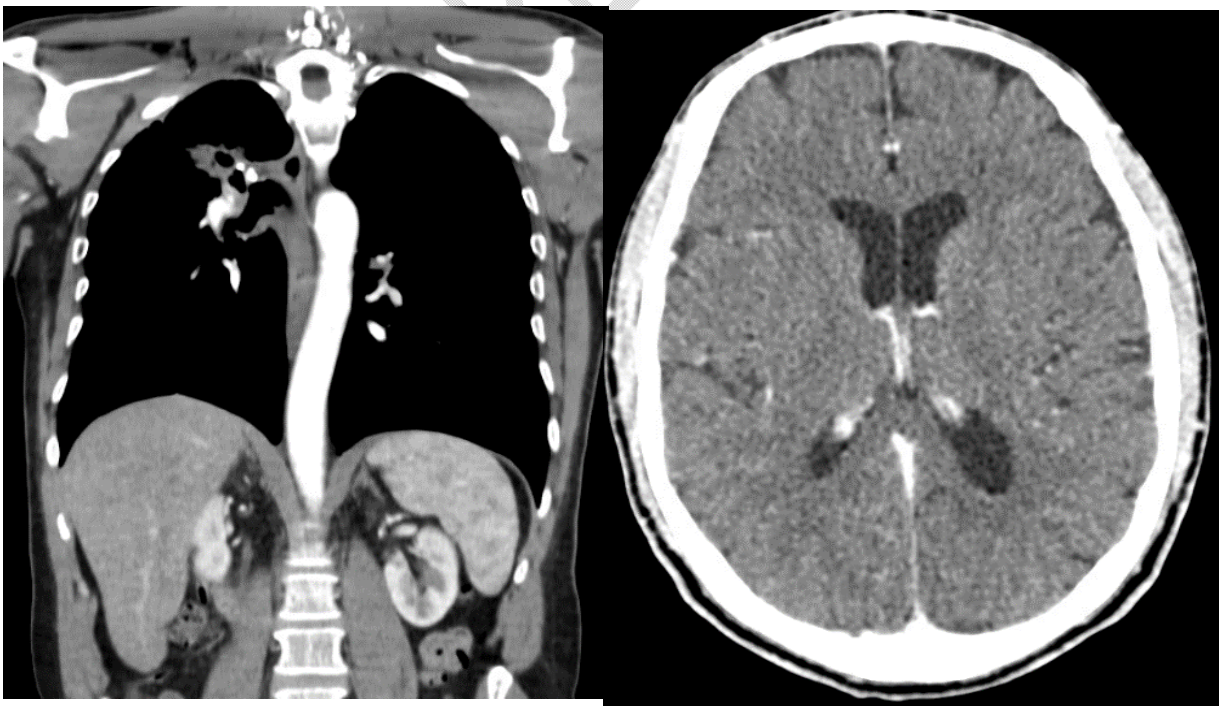

Figure 4: CT scan of the head and body conducted in 2019

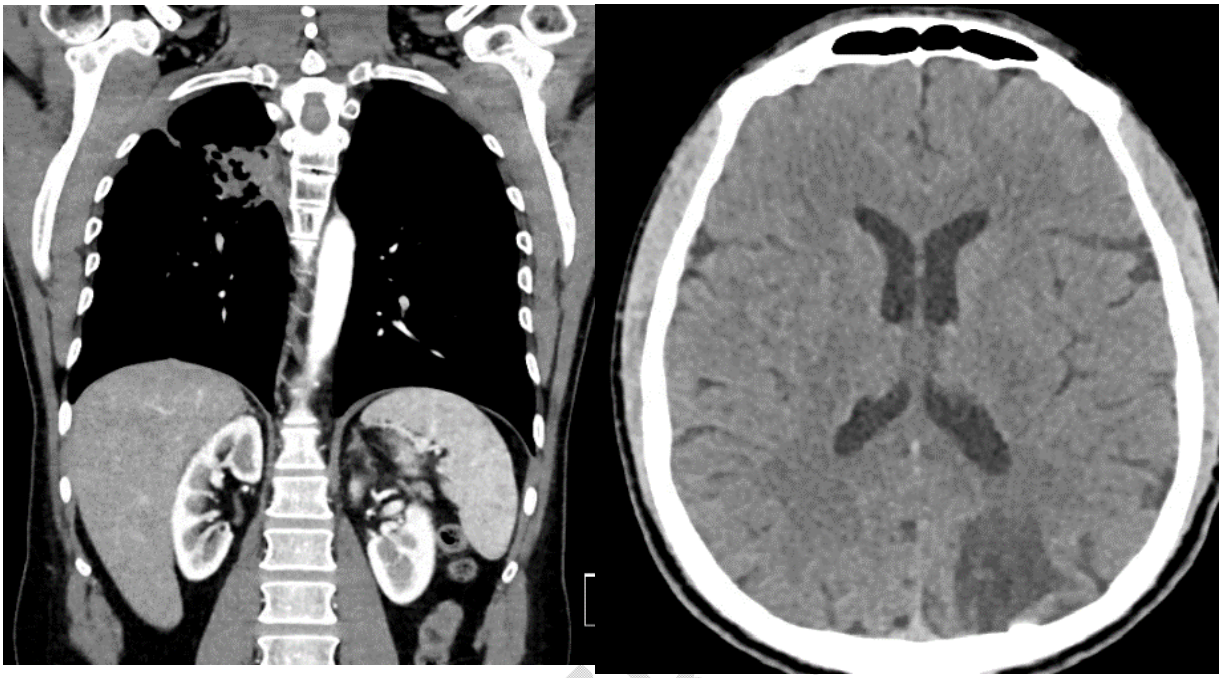

Figure 5: CT scan of the head and body conducted in 2020

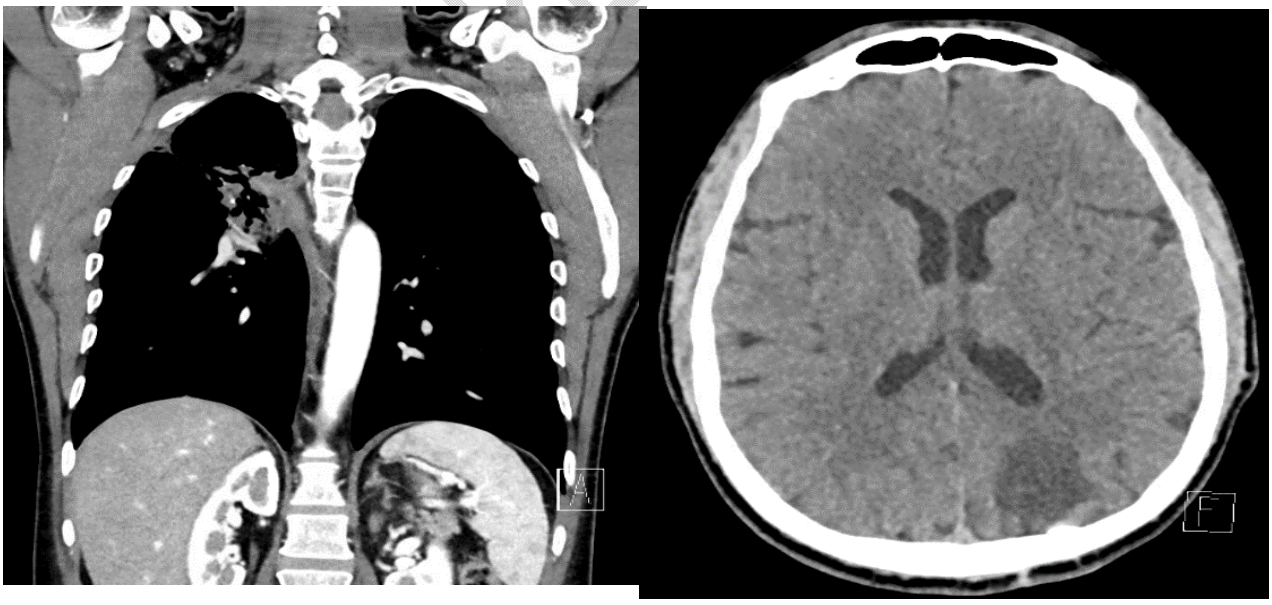

Figure 6: CT scan of the head and body conducted in 2021

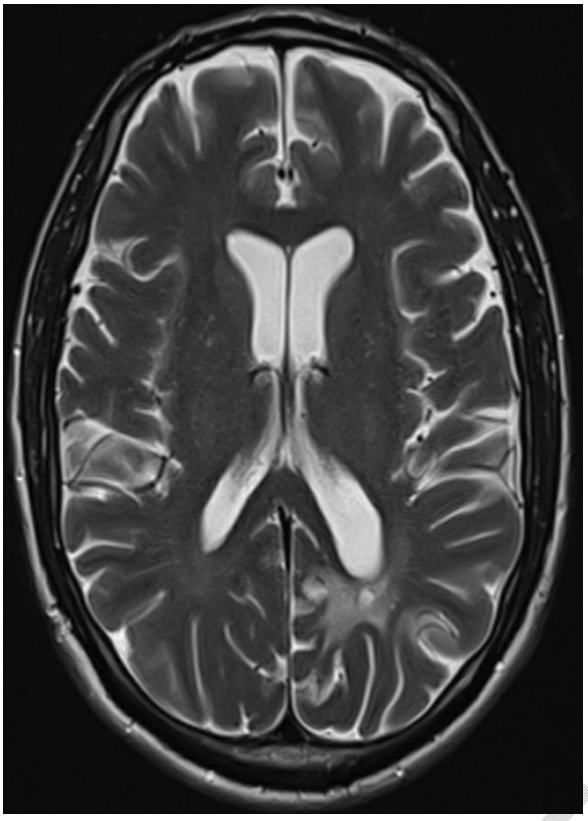

Figure 7: MRI of the brain, 2022

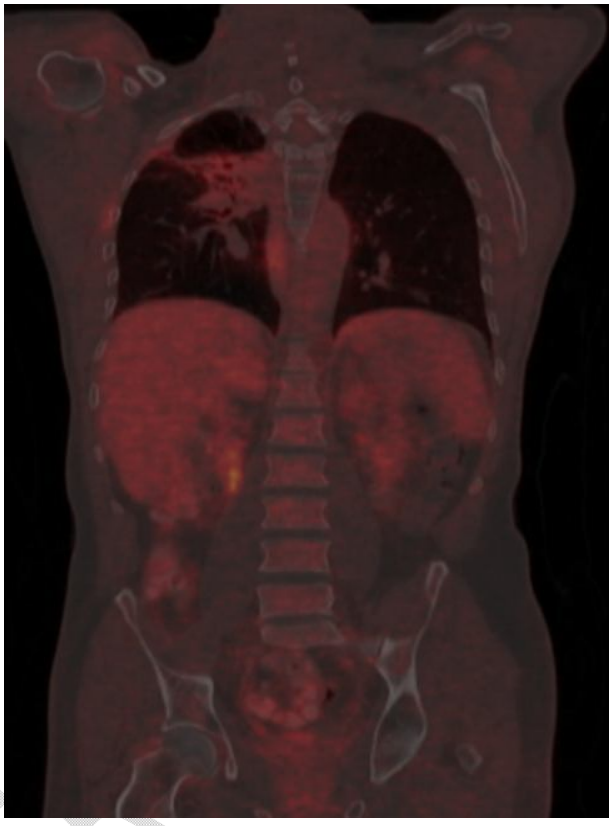

Figure 8: PET scan, 2022

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