

CLINICAL VIGNETTE

Autoimmune Pancreatitis and Immunotherapy

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A 66-year-old female presented with a new diagnosis of lung cancer. The patient was asymptomatic, but had a 40 pack-year smoking history and had lung cancer computed tomography (CT) lung screening. Imaging noted a 2.3-centimeter right lower lobe nodule invading the posterior right hilum. There were additional scattered nodules concerning but not definitive for metastatic disease. Nothing was noted on visualized abdominal sections. Positron emission tomography (PET) only showed the hypermetabolic right lower lobe lesion. Endoscopic bronchial ultrasound with biopsy of a level 7 node showed metastatic adenocarcinoma consistent with pulmonary origin. The cells were TTF1-positive and CK7-positive. Brain magnetic resonance imaging was unremarkable for metastatic disease. She unfortunately had significant delay between her imaging and follow up with her oncologist. Due to concern of further progression during this interval, repeat CT Chest noted progression of her right lung mass and growth of the previously noted pulmonary nodules, which suggested the lesions were truly metastatic disease. New retrocaval lymphadenopathy was also noted. Her pathology was sent for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS1 mutation testing and was negative for all. Her PDL1 expression was 70%. In terms of her past medical history including hypertension, hemochromatosis without need for treatment, hepatitis C with completion of prior treatment and negative viral load, irritable bowel syndrome, and fatty liver.

She presented for oncology second opinion and given her high PDL1 expression, immunotherapy with pembrolizumab every 3 weeks was recommended. She started treatment with minimal toxicity. She had a history of chronic diarrhea due to her irritable bowel syndrome, but no major changes with initiation of therapy. Exam and labs remained unremarkable.

After her sixth cycle, PET noted a decrease in the size of her right hilar pulmonary lesion, resolution of the pulmonary metastases, and a new subcarinal node of unclear significance. Given overall favorable response, she continued with pembrolizumab.

After cycle eight, she noted increasing abdominal girth and pain. Her diarrhea also increased. She was admitted to the hospital, where abdominal imaging noted signs of enterocolitis. She had a history of *Clostridium difficile* colitis in the past but workup for infection was negative. Colonoscopy with biopsy showed findings consistent with immune-mediated colitis. She

was started on steroids, with rapid improvement in her symptoms.

Upon discharge, the patient was not compliant with her steroid taper and stopped treatment almost immediately. Upon presentation to her oncologist, her diarrhea lingered slightly but did resolve. However, she now had a new significant epigastric pain and blood sugars trended up to the 300s. Repeat PET with diagnostic CT Abdomen and Pelvis showed diffuse hypermetabolism of the pancreas with nothing noted on CT. Her lung lesion and lymph nodes had decreased hypermetabolic activity. Amylase and lipase were elevated at 204 and 599. She was monitored by gastroenterology with eventual normalization of her labs with conservative measures. She was started on insulin due to persistent elevations of her blood sugars. Her epigastric pain slowly improved with time. Workup of her pancreatitis did not demonstrate any secondary causes.

Immunotherapy, particularly checkpoint inhibitors such as pembrolizumab, has become an exciting treatment modality for many malignancies including lung cancer.^{1,2} In general, programmed cell death receptor 1 (PD1) binds its ligands such as PDL1, leading to cessation of an immune response.³ Tumor cells can express PDL1 as a way of evading the immune system.³ Pembrolizumab is a monoclonal antibody to PD1 that blocks this binding and consequently overcomes this tumor cell resistance.³

Our patient's high PDL1 tumor expression indicated a high likelihood of response as noted on her follow up imaging. While this therapy generally is less toxic than cytotoxic chemotherapy, unfortunately, there is a small risk of autoimmune phenomena, most commonly colitis, hepatotoxicity, endocrinopathies, and dermatologic.¹ Rarer sequelae include pneumonitis and pancreatitis.^{1,2} The latter has been noted in <1% of patients treated with pembrolizumab or its sister drug, nivolumab.¹ Interestingly, unlike with other causes of pancreatitis, stranding and other radiologic features may not be noted on routine CT and MRI imaging.¹ For this reason, it may have been missed on her hospital imaging. However, it was clearly noted and new on her PET imaging upon discharge and amylase and lipase were certainly consistent with the diagnosis. As with most of the autoimmune toxicities, high-dose steroids are recommended.¹ The patient terminated steroid treatment early which may have allowed further inflammation after initial improvement. The colitis did not appear on outpatient CT imaging after hospital discharge.

There have been reports of pancreatitis noted incidentally on imaging, on patients clinically asymptomatic.^{1,2} The imaging findings were confirmed with abnormal amylase and lipase in these accounts.¹ Some reported, later imaging did eventually show pancreatic inflammation.² The mechanism of anti-PD1 immune-mediated pancreatitis is unknown.^{1,2} It is also unclear if stopping checkpoint inhibitors is enough to stop auto-immune pancreatitis once the process has begun.²

In the case above, given the patient's controlled lung cancer and significant life-threatening issues with pancreatitis, her therapy was held. Many patients maintain long-term control of their malignant disease after immunotherapy so expectant management was planned.

REFERENCES

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