Title

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CLINICAL VIGNETTE

Immune Checkpoint Inhibitor (ICI) induced Myocarditis in a Patient with Lung Cancer

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A 53-year-old male presented with several days of generalized weakness. He also reported mild lightheadedness, headache, fatigue, and a ten-pound weight loss over the prior two weeks. He denied chest pain, palpitations, dyspnea, fever, or cough. His past medical history was significant for stage II B poorly differentiated adenocarcinoma of the left upper lungs diagnosed two years prior. He was treated with three cycles of neo-adjuvant carboplatin, pemetrexed, and nivolumab (opdivo®) completed 9 months prior. He underwent left upper lobectomy, and additional treatment with combination of cisplatin and radiation therapy and remained in remission. Additional past medical history included thyroid papillary carcinoma ten years prior, treated with thyroidectomy and radioactive iodine ablation on thyroid replacement of 180mg daily. He also had orthostatic hypotension (thought secondary to pemetrexed and radiation), controlled with midodrine 10mg bid, pre-diabetes, hyperlipidemia, benign prostatic hyperplasia, and obstructive sleep apnea. His family history was non-contributory and he denied substance abuse.

On examination, vital signs included temperature 98.6°F, blood pressure 133/70 mmHg, pulse of 74 beats per minute, respiratory rate 15 breathes per minute, and O_2 saturation of 97% on room air. The physical exam was unremarkable. Laboratory evaluation was notable for a white blood cell count of 5.8 x 109/L, glucose **508 mg/dL**, troponin high sensitivity **160ng/L** (N<14ng/L), BNP 10pg/mL, TSH 1.5 mIU/mL (N), ESR 2mm/hr, CRP less than 2.9mg/L, HbA1c **8.7%** (N<5.7%). His Cortisol, creatinine kinase, and chemistry panel were within normal limits. His electrocardiogram (EKG) revealed normal sinus rhythm, diffuse non-significant 0.5mm ST elevations inferiorly and laterally, with no PR depression or reciprocal changes. Chest X-ray had no acute abnormality and trans-thoracic echo was unremarkable. A cardiac magnetic resonance image (MRI) with and without contrast revealed subtle abnormal delayed myocardial enhancement of the mid infero-lateral and inferior wall, nonspecific/nonischemic pattern, suggestive of acute myocarditis. On echocardiogram, his left ventricular ejection fraction was estimated at 57%. Prior Computed Tomographic (CT) of his coronary arteries revealed 24% stenosis in the proximal left anterior descending artery (LAD) and 25-49% stenosis in the first septal perforator. His high sensitivity troponin peaked at 179ng/L (N<14ng/L). Given his MRI findings and prior nivolumab use, there was concern for immune checkpoint inhibitor (ICI) induced myocarditis. Patient was also found to have ICI induced type 1 diabetes with elevated HbA1c 8.7%. His C peptide was low with normal Glutamic acid decarboxylase antibody, islet antigen antibody, and acetylcholine receptor binding antibody. He was started on steroids and insulin and discharged on a prednisone taper (60mg daily, tapered by 10mg every 4 days) for the treatment of ICI myocarditis and insulin for the treatment of diabetes type I. Close cardiology and endocrinology follow-up were arranged.

Discussion

Nivolumab (opdivo) is an anti-programmed cell death protein 1 antibody (anti-PD 1) used in the treatment of many malignancies. It is characterized as and immune checkpoint inhibitors (ICIs). Nivolumab specifically works by binding PD-1 on the surface of lymphocytes, which allows the immune system to recognize and destroy malignant cells.[1]

ICIs can produce dramatic and long-lasting anti-tumor effects and have become staples of oncologic treatment. Details of ICI's mechanisms of action is beyond the scope of this report. It is important for internists to recognize that drug effects are dose and duration dependent in terms of both anti-neoplastic action and the occurrence of side effects and toxicity which can last well beyond their pharmacokinetic half-lives.[2,3] This has implications for future primary care visits and hospitalizations. Hospitalists and primary care physicians should be aware of acute and long-term side effects. They may affect any organ system due to off target immune related events. ICI's often play a role in metastatic cancer and are generally used in (neo) adjuvant settings. Their acute side effects are more common, but chronic immune-related adverse events (irAEs) are increasingly recognized in clinical practice affecting as many as 40% of patients.[4] Chronic irAEs affect the rheumatologic and endocrine systems, with impact on a diverse array of organs.[5] ICI induced cardiotoxicity may result in myocarditis, heart block, atrial and ventricular arrhythmias, pericarditis, or cardiomyopathy.[6] This discussion will focus on ICI induced myocarditis.

ICI induced myocarditis is rare, reported in 0.1-1% of patients. Unfortunately, it is associated with a high fatality rate of 25-50%.[7] Combination immune checkpoint inhibitor therapy is associated with higher fatality rates as compared to monotherapy.[7] Myocarditis may be difficult to diagnose given diverse presentation.[7] Presentations range from non-specific symptoms such as fatigue to chest pain or cardiogenic shock. Endomyocardial biopsy is considered the gold standard to confirm the diagnosis. However; it is rarely pursued given its invasive

nature.[8] Therefore, the incidence of IDI-induced myocarditis is likely under-estimated. Most reported cases of ICI induced myocarditis occur within the first six weeks to six months of treatment. Our patient presented nine months after his last dose. However, cardiotoxicity may be present in patients who are no longer actively taking ICIs. This is due to persistent occupation of the PD-1 receptors, even after completing treatment.[8] Pathophysiology of ICIs induced myocarditis is not well elucidated. Histologically the myocarditis has been described as lymphocytic myocarditis. Sobol, I. Chen et all studied six patients with biopsy proven ICI induced myocarditis and reported lymphohistiocytic myocarditis may be a more accurate description.[9] High dose steroids along with supportive care is the mainstay treatment for ICI induced myocarditis.[10] Duration of treatment and steroid taper is dependent on patients' clinical response. Serial troponins may be monitored and used to guide treatment.[10] Other immunosuppressants such as mycophenolate, infliximab, intravenous immunoglobulin, plasmapheresis have also been used.[10] They may be reserved for patients with an inadequate response to steroids. Effectiveness of these additional therapies is unclear.[10]

Patients with lung cancer may be at higher risk for developing pericarditis as their irAE.[11] Overall, pericardial inflammation tends to be more steroid responsive and less fulminant than myocarditis. Our patient presented with vague symptoms, which are common with myocarditis. He presented nine months after his last dose of opdivo, which is more delayed than the average onset of six weeks to six months reported in the literature. Initial clinical use of novolumab was associated with acute fulminant myocarditis. This was the most common cardiac side effect. Surveillance and recognition strategies have identified more subtle presentations. These include more chronic forms of myocarditis, including asymptomatic patients with and mild troponin elevations. It is uncertain if these patients are at increased risk for subsequent cardiomyopathy? The implications are of significant importance and are compelling reason for regular follow up visits, and ongoing trials.[12]

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