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Case: A Case of Pembrolizumab Induced Myocarditis and Complete Heart Block

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Abstract

Use of checkpoint inhibitor pembrolizumab has continued to grow since its approval in 2014. Rare instances of conduction side effects have been described including brady and tachyarrhythmias, heart block and even cardiac arrest. We present a case of Pembrolizumab induced myocarditis and persistent third-degree heart block.

Keywords: Pembrolizumab, Heart block

1. Background

Use of checkpoint inhibitor pembrolizumab has continued to grow since its approval in 2014. Rare instances of conduction side effects have been described including brady and tachyarrhythmias, heart block and even cardiac arrest. We present a case of Pembrolizumab induced myocarditis and persistent third-degree heart block.

2. Case

72 year male with history of B12 deficiency, osteoarthritis, COPD with 25 pack year of smoking but no known cardiac, autoimmune or rheumatological issues presented to his primary care physician with cough, dyspnea on exertion for 4 months and 10 pound weight loss. Chest x-ray showed 3.3 cm density on right upper lobe. Chest CT showed anterolateral right upper lobe pleural-based mass of 0.8 cm with spiculations. PET-CT showed hypermetabolic right upper lobe lesion with standard uptake value (SUV) of 6.73, left upper lobe nodule with SUV of 3.95, hypermetabolic right hilar, paratracheal and precarinal lymph nodes. CT-guided biopsy showed lung adenocarcinoma. EGFR/BRAF/HER2/KRAS/RET/MET amplification was negative. PDL1 was not expressed with tumor proportion score (TPS) < 1%. He was started on neoadjuvant chemo immunotherapy (pembrolizumab, carboplatin, pemetrexed). Three weeks later, he presented with diplopia, right ptosis, generalized fatigue and shortness of breath. He was afebrile and hemodynamically stable on room air. Labs showed normal proBNP, creatinine of 1 g/dl, BUN 20 mg/dl, potassium 5.3 meq/L, sodium 137 meq/L, total bilirubin of 0.7 mg/dl with direct of <0.2 mg/dl, AST 408 IU/L, ALT 164 IU/L, WBC 3.9, troponin I 1.11 ng/ml, TSH 1.33 IU/ml. INR, acute hepatitis panel and iron panel were normal. Influenza and COVID were negative. Chest x-ray showed no new acute cardiopulmonary disease. CT and MRI head showed no bleeding, enhancement or hyperintensity. Initial EKG was normal. Echo showed normal LV systolic function of 66%, grade 1 diastolic dysfunction and right ventricular pressure of 32 mmHg. By 2nd day, his LFT, CPK and troponin continued to worsen (AST 505 IU/L, ALT 443 IU/L, CPK 5550 IU/L, LDH >1000 IU/L, HS troponin 3168 ng/L). Further lab work showed ESR 28 mm/h,CRP<0.3 mg/dl, ANA 1:1640 (homogenous), antimitochondrial antibody 15.9 Units (Normal 0−24), antismooth muscle Ab 18 units (normal 0−19), IgG 2927 mg/dl (normal 700−1600), LKM IgG Ab <1:20 units, aldolase 116U/

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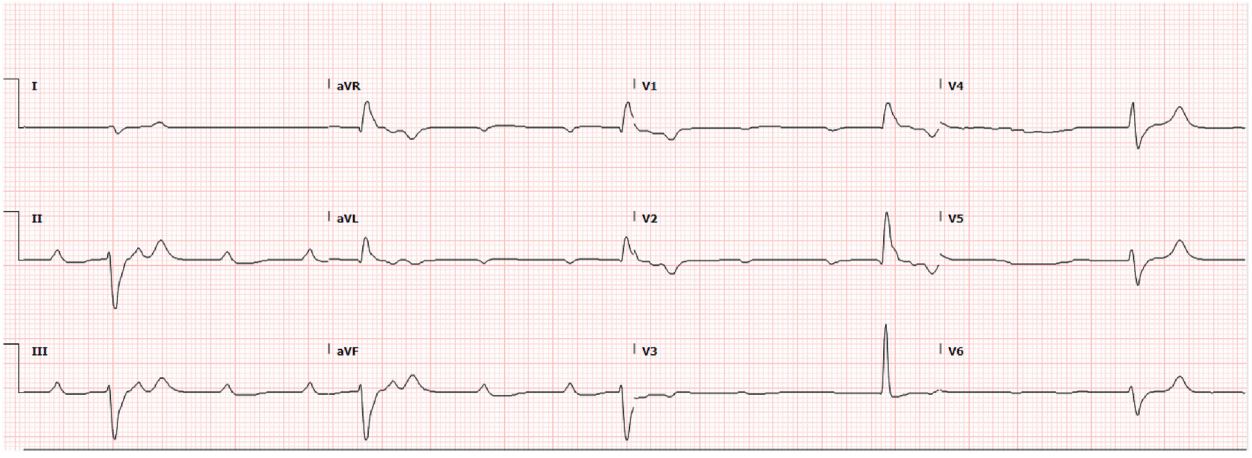
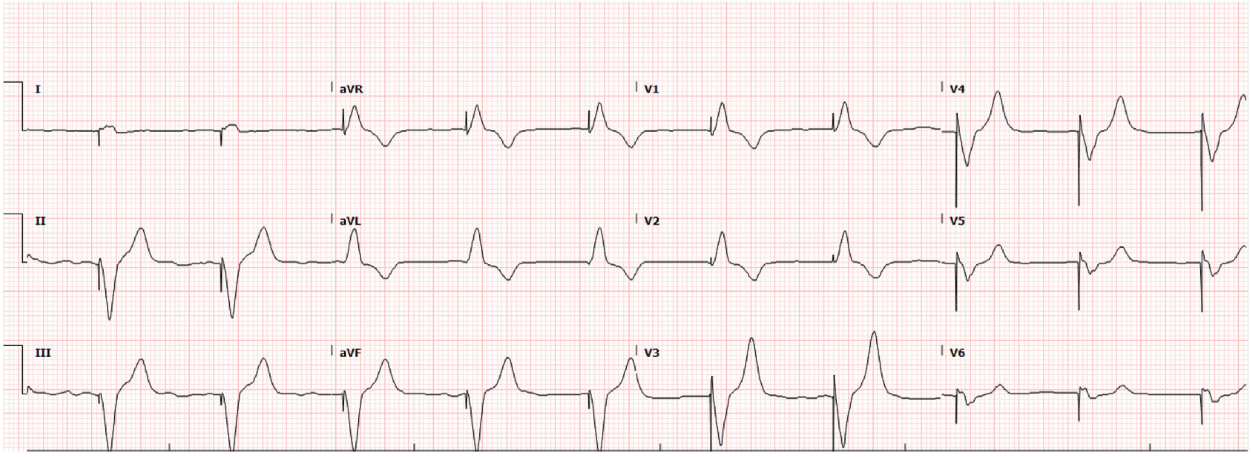
L (normal 1−7.5 U/L) and normal ACE level of 24 mcg/L. Abdominal and duplex ultrasound showed mildly echogenic and coarsened parenchyma with normal contour and no portal vein thrombosis. CT abdomen pelvis showed normal liver and biliary system with no ductal dilatation. Electrodiagnostic study showed no evidence of neuromuscular junction disorder or lumbosacral plexopathy/radiculopathy. On the 3rd day, he developed progressive bradycardia followed by 2:1 AV block, nonsustained ventricular tachycardia and frequent premature ventricular contractions. He then had 12 s pause on telemetry and subsequently complete heart block with ventricular escape (EKG 1−3).

He was started on IVIG 0.4 gm/kg for possible myasthenia gravis and Solu-Medrol 2 mg/kg for immune checkpoint related myocarditis. He underwent emergent transvenous pacemaker (TVP) and plasmapheresis for 5 sessions given no improvement with IVIG. His acetylcholine blocking antibodies, MUSK Ab, voltage gated calcium channel and ganglioside (GM1, GD1b, GQ1b) came back as normal. After these treatments, his ptosis on the right eye improved and diplopia completely resolved. Patient continued to be in complete heart block and TVP dependent after which mycophenolate was started and had a leadless pacemaker. Unfortunately, his LFTs and HS troponin continued to rise (AST and ALT >500IU/L, HS Troponin at 3940 ng/L) but CPK did decrease to 3700 IU/L. While a second immunosuppressive was planned, patient elected to be discharged back home on hospice and passed within a day of discharge.

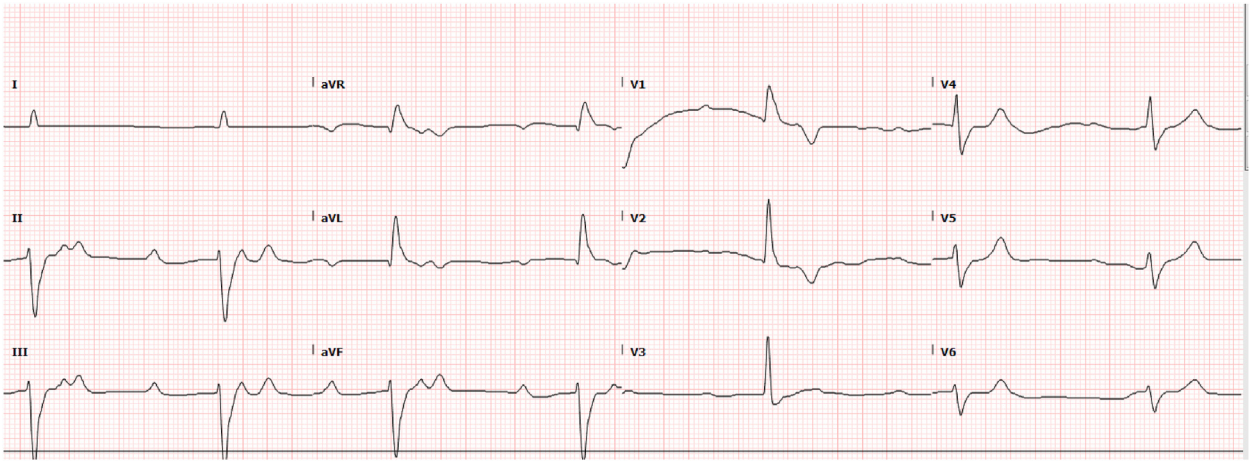
EKG1: Complete heart block, normal sinus rhythm with ventricular escape.



EKG2: Ventricular paced rhythm after TVP.



EKG3: High degree AV Block.



3. Discussion

Pembrolizumab is an immunized monoclonal IgG4 antibody directed against programmed death-1(PD-1). Since its approval in United states in 2014, its clinical use has continued to expand and is being used in various cancers. Pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells and blocks the binding to and activation of PD-1 by its ligands which then results in activation of T-cell-mediated immune responses against tumor cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1) overexpressed on certain cancer cells and programmed cell death ligand 2 (PD-L2) which is primarily expressed on antigen presenting cells. Enhanced immune activation by a PD-1 inhibitor can induce serious immune-related adverse events (irAEs). Cardiac irAEs include myocarditis, heart failure, myocardial infarction, takasubo cardiomyopathy, pericardial disease, coronary vasospasm and arrythmias.[1] Among these side effects, myocarditis is most common with an incidence of about 1–2%.[1-4] Most cases of immune checkpoint inhibitor (ICI) myocarditis occur within first or second infusion (between 30 and 65 days) but can have large variations.[3,4] Despite its low incidence, ICI myocarditis has one of the highest fatality rates of all cases of irAEs, with mortality of>50%.[5] Among biomarkers, high LDH level and CPK concentrations>3 × upper level of normal has been linked with greater mortality.[6]

Myocarditis is usually associated with increased AST, ALT, LDH, ESR, CRP and CPK. Diagnosis can be challenging especially in the early phase of disease. Clinical, histological, immunological and immunohistochemical criterias have been developed for diagnosis of ICI myocarditis (Fig. 1).[7] Clinical manifestations of immune-related myocarditis are variable ranging from nonspecific symptoms like fatigue, chest pain, palpitation and heart failure symptoms. Most patients present with an abnormal electrocardiogram (ECG), elevated troponin along with elevated biomarkers as mentioned above. Clinically myocarditis is

Clinical features:
-Chest pain, shortness on breath and signs of heart failure
-Palpitation, arrhythmias, syncope, cardiogenic shock
Diagnostic modalities:
-EKG changes like atrioventricular blocks, T-wave changes ventricular tachycardia or fibrillation, supraventricular tachycardia, asystole, low-voltage, abnormal Q-waves
-Ventricular tachycardia or fibrillation, supraventricular tachycardia, asystole, low-voltage, abnormal Q-waves
-Troponin leak, wall motion abnormalities, global systolic or diastolic dysfunction, right or left ventricular dysfunction on echocardiogram or cardiac MRI

Fig. 1. Clinical features and diagnostic modalities of immune checkpoint inhibitor myocarditis.

suspected when 1 clinical feature and >1 diagnostic criteria are met.[5] If patient are asymptomatic, >2 diagnostic criteria are required for the diagnosis.[7]

Echocardiographic examinations in the early stages of myocarditis can be normal or can have transient wall thickening with edema, impaired ventricular function or ventricular dilation. Cardiac MRI (cMRI) is considered superior to echocardiography as it provides better tissue characterization like edema, necrosis, and scar formation but also can be normal in early phase of disease.[8] Non Invasive diagnosis of myocarditis with cMRI ("Lake Louise Criteria") has been established by the international consensus group.[8] If MRI is contraindicated or not available, cardiac FDG-PET-CT can also be used to assess inflammation.

Exact mechanism for immune checkpoint inhibitor-mediated arrythmias is not well known but few possible mechanisms have been postulated like shared antigen theory.[9] On animal models, PD-1 appears to protect against tissue inflammation and its deletion appears to correlate with autoimmune myocarditis.[10] In mouse models, myocardial PD-L1 up-regulation is noted in autoimmune myocarditis likely a cardio-protective mechanism and the upregulation is critical for limiting immune-mediated cardiac injury that can be inhibited by anti-PD-L1 antibody.[10]

Combination of ICI appears to be the most common risk factor for ICI induced myocarditis and other conduction abnormalities in the heart however hypertension, diabetes, pre-existing heart disease can also contribute.[4,9]

Guidelines recommend discontinuation of ICI therapy and treatment with high-dose corticosteroids.[9-11] If steroids are ineffective, other immunosuppressive agents like, antithymocyte globulin, mycophenolate mofetil, infliximab, tacrolimus, alemtuzumab, tocilizumab, rituximab have been recommended.[10,11] Although there are no clear guidelines about the duration of steroids or immunosuppressives, treatment is continued until resolution of symptoms and normalization of cardiac troponin, ejection fraction or conductions issues. Biomarkers may remain elevated for months after treatment however CPK tends to have a rapid decline which may be useful to access treatment effectiveness.[6] Whether or not ICI can be reused later is unclear but successful rechallenge with ICI after cured ICI-induced myocarditis has been described in literature.[12] Life vest in patients with severe ventricular arrhythmias can be used while waiting for myocarditis to improve.[13] ICD implantation is not routinely recommended until resolution of the acute episode as myocarditis may heal completely.

4. Conclusion

Checkpoint inhibitors do have various toxicities including myocarditis, arrythmias, hemiblock or complete heart block. High index of clinical suspicion for irAEs is essential in the era of rising immunotherapy use especially given high mortality rate. Early detection with multidisciplinary involvement is crucial.

Conflict of interest

No conflict of interest.

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