Pembrolizumab-Induced Triple M Syndrome in a Patient with Stage III Melanoma: A Case Report

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized oncology. While pembrolizumab shows considerable antitumor effects, it is also associated with serious and potentially life-threatening side effects.

One of the more severe reactions is a rare overlap syndrome that includes myocarditis, myositis, and myasthenia gravis (MG), referred to as IM3OS, for which there is limited data available.

Case presentation

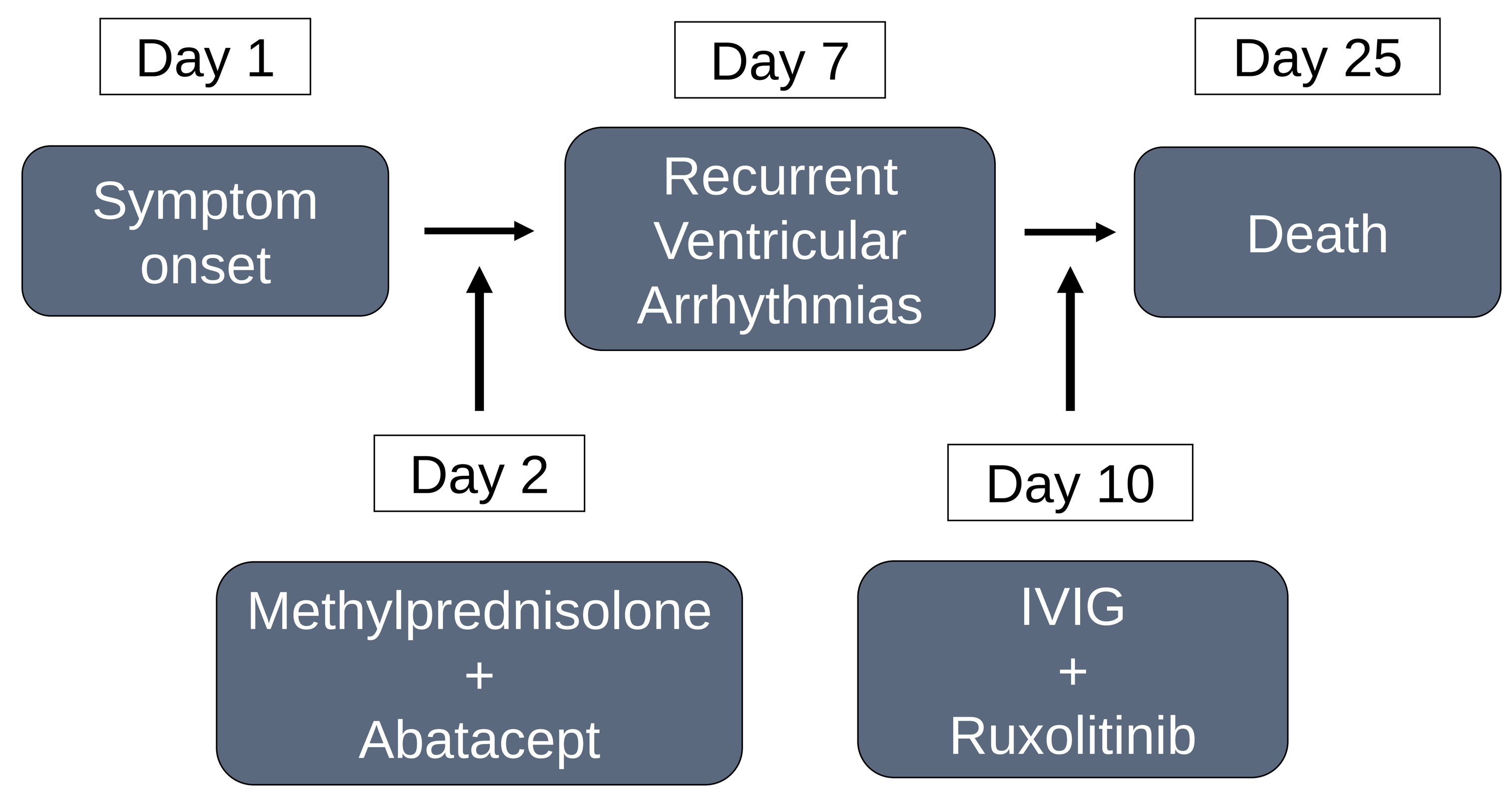
A 70-year-old male patient with stage III melanoma, treated with surgical resection and pembrolizumab, presented with diplopia and ptosis.

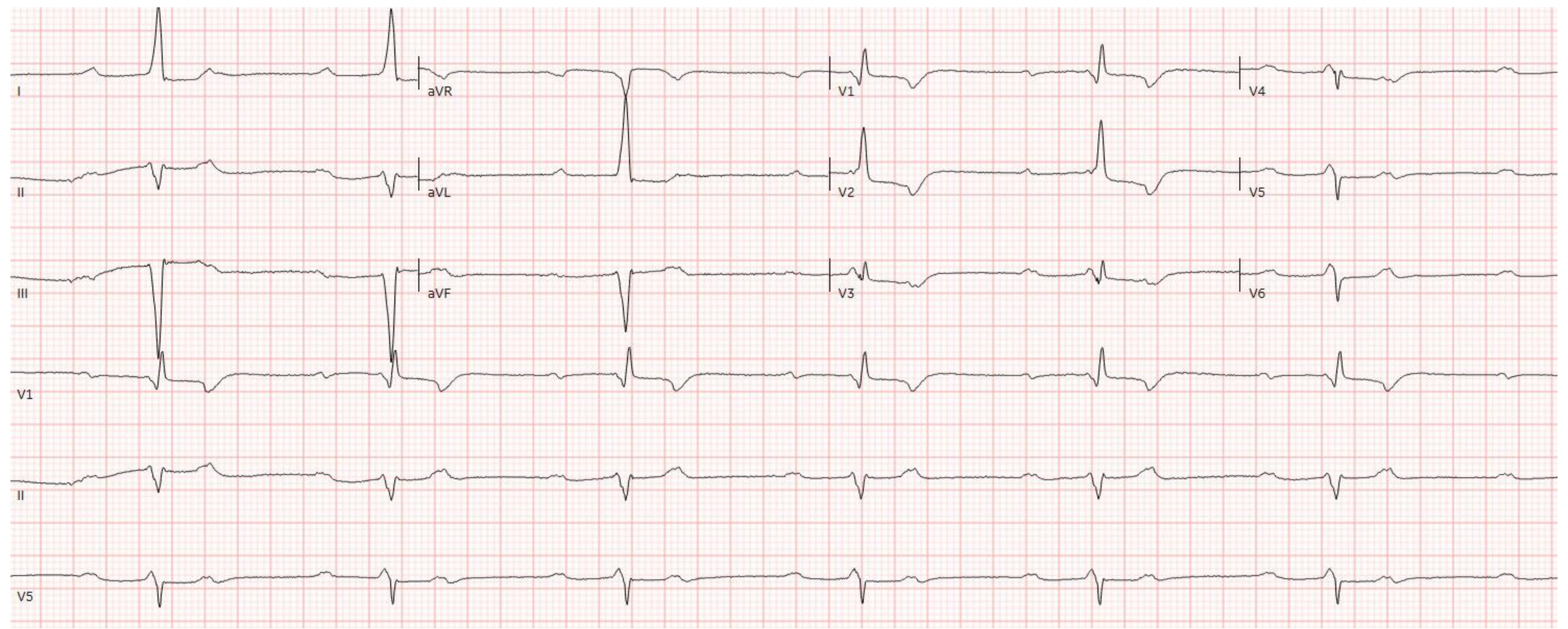
Initial electrocardiogram indicated a complete heart block requiring the insertion of a pacemaker.

ICI-induced myocarditis was suspected. Methylprednisolone pulse and Abatacept therapy was started, resulting in some improvement in his weakness, although muscle enzyme levels continued to be elevated. Patient was transferred to another facility, where he received intravenous immunoglobulin (IVIG) and ruxolitinib. Unfortunately, he later passed away due to ventricular arrythmias.

Laboratory	Value	Units
Troponin	20,120	ng/L
Creatinine Kinase	12,429	U/L
Aldolase	119.4	U/L
Acetylcholine Receptor Binding AB	0.65	Nmol/L
Acetylcholine Receptor Modulating AB	<1	%
Anti Muscle Specific Kinase	Negative	

Case presentation





Discussion

The exact incidence of overlap syndrome is uncertain. Some systematic reviews indicate low rates of immune ICI-related MG and myocarditis. However, myocarditis presents a mortality rate as high as 50% with a median onset of 30 days following the start of therapy.

Some evidence suggests that early intervention with corticosteroids and in IVIG may enhance patient outcomes. Additionally, the use of IVIG and plasmapheresis could decrease mortality.

In our case, a delay in starting IVIG may have influenced the clinical results.

Conclusion

This case highlights the importance of vigilant monitoring and early detection of these potentially fatal complications. While documentation on immune-related adverse events (IRAEs) is extensive, description of the triple M overlap syndrome remains limited, emphasizing the need for further research.

References

Safa H, Johnson DH, Trinh VA, et al. Immune checkpoint inhibitor-related myasthenia gravis: single-center experience and systematic review of the literature. J Immunother Cancer. 2019;7(1):319. doi:10.1186/s40425-019-0774-y. PMID: 31753014; PMCID: PMC6868691.

Palaskas N, Lopez-Mattei J, Durand JB, et al. Immune checkpoint inhibitor myocarditis: pathophysiological characteristics, diagnosis, and treatment. J Am Heart Assoc. 2020;9(2):e013757. doi:10.1161/JAHA.119.013757.

Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4(12):1721-1728. doi:10.1001/jamaoncol.2018.3923. Erratum in: JAMA Oncol. 2018;4(12):1792. PMID: 30242316; PMCID: PMC6440712.

Hu JR, Florido R, Lipson EJ, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovasc Res. 2019;115(5):854-868. doi:10.1093/cvr/cvz026. [Published correction appears in Cardiovasc Res. 2019 Apr 15;115(5):868. doi:10.1093/cvr/cvz082.]

Soman B, Dias MC, Rizvi SAJ, Kardos A. Myasthenia gravis, myositis, and myocarditis: a fatal triad of immune-related adverse effect of immune checkpoint inhibitor treatment. BMJ Case Rep. 2022;15(12):e251966. Published December 8, 2022. doi:10.1136/bcr-2022-251966

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