Background Immune checkpoint inhibitors (ICls) can lead to immune-related adverse events (irAEs). One such irAE, ICI-induced autoimmune diabetes (ICI-DM), affects approximately 1% of ICI recipients. Most reports suggest resemblance to fulminant type 1 diabetes, with low or absent endogenous insulin production at presentation. However, more recent reports have revealed milder cases, suggesting a heterogeneous disease entity. We identified distinct clinical phenotypes of ICI-DM that could allow for better optimization of insulin therapy.

Methods We performed a retrospective chart review of 16,582 patients treated with anti-PD1, anti-PDL1, anti-CTLA4, or combination between 2010 and 2022 at a multi-centered academic hospital system. Criteria for inclusion were new diagnosis of type 1 diabetes or drug-induced diabetes and new prescription for insulin following ICI therapy; cases were confirmed by two board-certified endocrinologists. To phenotype ICI-DM based on endogenous insulin production, we reviewed patients with ICI-DM and a C-peptide level, allowing us to classify 45 cases of ICI-DM based on endogenous insulin production and autoantibody status. We are characterizing ICI-DM in these patients at both initial presentation and up to 30 months of follow-up.

Results We identified three distinct clinical phenotypes of ICI-DM based on initial presentation: patients with preserved endogenous insulin production (insulin+), patients with decreased or absent endogenous insulin production (insulin-), with the latter divided into autoantibody-positive (Ab+) and negative (Ab-) patients. Insulin+ ICI-DM patients have high levels of pre-existing insulin resistance, longer time-to-diagnosis (median 175 days), higher A1c at presentation (median 9.8%), and lower likelihood of presenting in diabetic ketoacidosis (DKA). Insulin-Ab+ patients have lower levels of insulin resistance, the lowest time-to-diagnosis (median 65 days), intermediate A1c at presentation (median 8.2%), high rates of DKA and nearly universal hospitalization at presentation. Insulin-Ab- had no pre-existing insulin resistance, a longer time-to-diagnosis (median 154 days) with a relatively low A1c at presentation (median 7.6%), and moderate rates of DKA and hospitalization. As expected, insulin- patients had higher total daily insulin needs compared to insulin+ patients.

Conclusions Our study examined the largest data set to date of deep clinical phenotyping of patients with ICI-DM. We define at least two distinct subsets of ICI-DM, with antibody-positive, islet negative patients being most similar to cases of ICI-DM initially described. However, patients with a milder form of ICI-DM (islet positive patients) may require simpler insulin regimens that could profoundly improve their quality of life. Our findings may also suggest distinct underlying mechanisms for ICI-DM with implications for other irAEs.

REFERENCES

Ethics Approval This study was approved by the Mass General Brigham Institutional Review Board, Protocol #2017P000501. There was no direct interaction with patients or their samples so individual consent was not deemed necessary by the IRB.