the authors) could be involved in such a condition, it would be interesting to recheck the patients' serum for the presence of circulating ACTA using an indirect immunofluorescence assay, as described by our group.[2] A possible immune response against the conductive system is suggested by the reported lymphocytic infiltrate involving the cardiac sinus, the atrioventricular node, and the esophageal muscle. In our study, the patient with circulating ACTA had not only heart block but also intestinal pseudo-obstruction, with the latter probably caused by an impairment in the "gut pacemaker" and intestinal conductive system.[3]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We completely agree with Ederhy and colleagues that cardiac complications are rare with immune checkpoint inhibitors when the drugs are used as single agents. However, our current data suggest that such complications may be more frequent with combination therapy and that simple cardiac screening may be appropriate. There are several important considerations regarding the cardiovascular safety data generated from oncology clinical trials, as Ederhy et al. have compiled in Table 1 of their letter. First, oncology trials often exclude "real world" patients who have a previous cardiac history and may be at increased risk for cardiac complications. Second, there are inherent limitations in the manner in which cardiac toxicity is adjudicated in oncology trials. Almost no checkpoint-inhibitor trial to date has screened patients for myocarditis. Third, myocarditis is often a diagnosis of exclusion and can be missed if there is no active monitoring for this toxicity. Finally, the cases of myocarditis associated with checkpoint inhibitors that we have seen are characterized less by the typical features of cardiomyopathy and more by electrocardiographic instability, which may be more difficult to detect.

Caio's point is well taken regarding the possibility of detection of autoantibodies in our patients. However, it is important to note that the presence of autoantibodies does not prove causation. In our patients, we looked for antibody deposits in the inflamed tissues but did not find any evidence of antibody deposition. Instead, we observed a dense cellular infiltrate composed of T cells and macrophages in the heart and skeletal muscle. We certainly agree that further research in this area should include a detailed analysis of circulating antibodies.

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Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at *PRNP* Codon 129

TO THE EDITOR: Prions cause lethal neurodegenerative diseases in mammals and are composed of multichain assemblies of misfolded host-encoded cellular prion protein (PrP). A common polymorphism at codon 129 of the PrP gene (*PRNP*), where either methionine (M) or valine (V) is encoded, affects the susceptibility to prion disease, as well as the incubation period[1] and clinical phenotype of prion disease. Human infection with the epizootic prion disease bovine spongiform encephalopathy resulted in variant Creutzfeldt–Jakob disease, which provoked a public health crisis in the United Kingdom and other regions. All definite cases of variant Creutzfeldt–Jakob disease to date have occurred in patients with the MM genotype at *PRNP* codon 129.[1]

A 36-year-old man was referred to the United

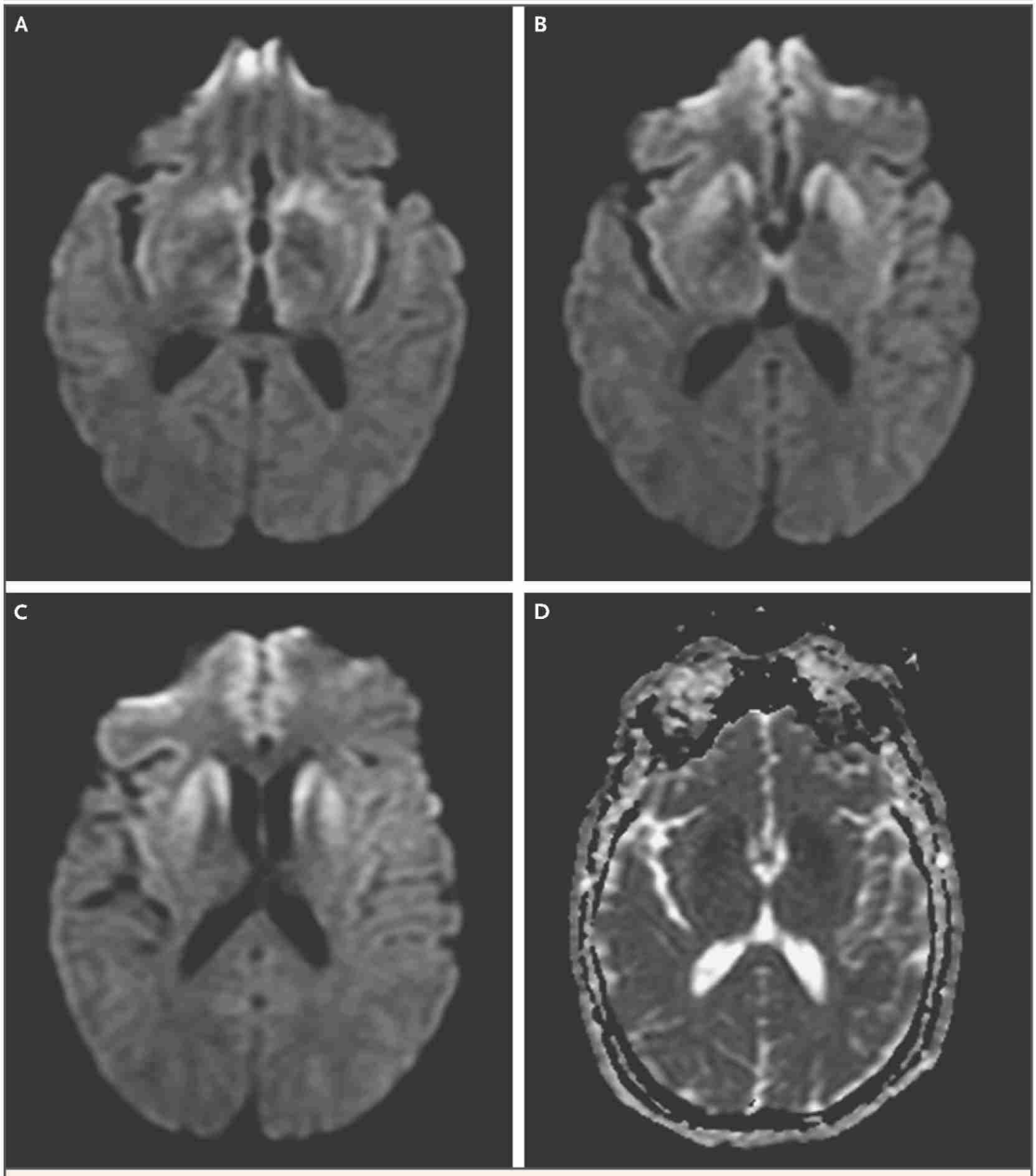

Figure 1. MRI of the Brain.

Trace-weighted diffusion-weighted images (Panels A, B, and C) show high signal intensity in the basal ganglia, hypothalami, and medial thalami but not in the pulvinar nuclei. These structures appear dark on the apparent diffusion coefficient map (Panel D), thus confirming the presence of restricted diffusion.

Kingdom National Prion Clinic in August 2015 with personality change. Over a period of 9 months, he had become uncharacteristically irascible and had progressive episodic memory impairment, gait ataxia, and myoclonus. His score on the Mini–Mental State Examination was 25 (with scores ranging from 0 to 30 and higher scores indicating less impairment); clinical examination revealed extraocular eye-movement abnormalities, pyramidal and cerebellar signs, and multifocal myoclonus. Magnetic resonance imaging of the brain (Fig. 1) revealed restricted diffusion in the basal ganglia, hypothalami, insular cortexes, and medial thalami but not in the pulvinar nuclei.[2] Examination of the cerebrospinal fluid for protein 14-3-3 was nega-

tive, as was a real-time quaking-induced conversion assay, although these two tests are known to have low sensitivity for variant Creutzfeldt–Jakob disease.[3] His genotype at *PRNP* codon 129 was MV. During the following 6 months, the patient's condition declined progressively, and severe dysphagia and agitation occurred shortly before his death in February 2016.

At autopsy, histologic examination of the brain revealed frequent florid and cluster plaques in cerebral and cerebellar cortexes, microvacuolar degeneration in neuropil, and immunostaining for abnormal PrP in a stellate pericellular and perivascular distribution. Minute amounts of protease-resistant PrP (PrP^{Sc}) were seen in lymphoid tissue of the spleen. Immunoblotting of brain homogenate revealed type 4 PrP^{Sc} (according to the London classification system), which is pathognomonic of variant Creutzfeldt–Jakob disease.[4] (For more details, see the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

This patient's clinical features differed from those of typical variant Creutzfeldt–Jakob disease, and his neuroimaging features suggested a diagnosis of sporadic Creutzfeldt–Jakob disease. He did not meet the epidemiologic diagnostic criteria for probable or possible variant Creutzfeldt–Jakob disease,[5] yet the results of the neuropathological examination and molecular strain typing were consistent with variant Creutzfeldt–Jakob disease. It remains uncertain whether this case marks the start of a second wave of variant Creutzfeldt–Jakob disease in persons with the MV genotype at *PRNP* codon 129 (the most common genotype in the United Kingdom), mirroring the long incubation periods seen in persons with the MV genotype who have other acquired prion diseases, notably kuru.[1] This case emphasizes the importance of performing an autopsy and molecular strain typing in cases of prion disease to ascertain the prevalence of human prion disease related to bovine spongiform encephalopathy.

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