Immune checkpoint inhibitor rechallenge in patients with immune-related myositis

Therapeutic management of many cancers has been revolutionised by the development of immune checkpoint inhibitors (ICI) targeting antiprogrammed death 1 (PD-1)/ligand 1 (PDL1) and anticytotoxic T-lymphocyte antigen 4 leading to durable responses.[1] ICIs however can induce several immune-related adverse events (irAE) including musculoskeletal irAEs.[2] Among them, ICI-related myositis can be severe and sometimes life threatening.[3 4] The current management includes permanent discontinuation of ICIs and steroid treatment. To date, very little is known about the risk of irAE recurrence in case of ICI rechallenge,[5 6] especially in myositis for which no case of rechallenge has yet been reported. Through two cases, we report the safety of resuming anti-PD-1/PDL1 in patients who experienced severe ICI-related myositis.

An 87-year-old patient with metastatic Merkel cell carcinoma (MCC) received avelumab as first-line treatment. After three infusions, he developed slight head dropped syndrome with increased creatine kinase (CK) level up to 3.5 times the upper limit normal (ULN) range. Electromyography showed myogenic syndrome (left trapezius and right sternocleidomastoid muscles) and ^{18}F-fluorodeoxyglucose-positron emission tomography revealed significant hypermetabolism of axial muscles (table 1). Myositis-specific autoantibodies were negative. Myocarditis was ruled out. At that time the radiologic evaluation showed a partial tumour response. Avelumab was stopped and the patient received prednisone (tapering from 0.5 mg/kg) during 6 weeks, which allowed myositis remission, but MCC recurred 7 months later. Avelumab was resumed and prednisone was preventively given during 3 months, starting at 20 mg/day. With a 9-month follow-up, no irAE, including myositis, occurred and MCC returned in partial response.

A 61-year-old patient with metastatic melanoma developed ptosis, diplopia, dysphagia and muscle weakness 3 weeks after first infusion of ipilimumab combined with nivolumab as first-line treatment. CK levels raised up to 40 ULN. Electromyography showed myogenic pattern of the trapezius, without decrement. Muscular biopsy with focal necrosis/regeneration lesions, HLA-1 and C5b9 positive sarcoplasmic staining of the suffering myofibres and T cell infiltrates confirmed the myositis.

Table 1 Patient characteristics

		Patient 1	Patient 2
Cancer history	Stage IV cancer	Merkel cell carcinoma	Melanoma
	ICI	Avelumab 10 mg/kg/2 weeks, 3 infusions	Ipilimumab 3 mg/kg+nivolumab 1 mg/kg, 1 infusion
ICI-related myositis	Onset of symptoms	Week 6	Week 3
	Clinical symptoms	Dropped head syndrome	Myalgia, muscle weakness
		Neck pain	Ptosis, diplopia, dysphagia
		Fatigue	Fatigue
	Maximum Creatine kinase	×3.5 ULN	×40 ULN
	Electromyography	Myogenic syndrome: Left trapezius and right sternocleidomastoid muscle. No decrement.	Myogenic sundrome: Right trapezius. No decrement.
	FDG-PET	Significant hypermetabolism of trapezius, erector muscles of the spine, pilar muscle of the diaphragm	Slight diffuse muscular hypermetabolism
	Muscular biopsy	Contraindication (anticoagulant treatment for atrial fibrillation)	Positive with focal necrosis/regeneration lesions, HLA-I and C5b9 positive staining, presence of T cell and macrophage inflammatory cells
	Cardiac examination ECG	Permanent atrial fibrillation (>5 years)	Normal
	High-sensitive troponin-T (<14 ng/L)	475	298
	Echocardiography	Normal	Normal
	Cardiac MRI	Contraindication (pacemaker)	–
	Cardiac FDG PET	No myocarditis	No myocarditis
	Treatment of irAE	Oral prednisone 0.5 mg/kg/day, tapered and withdrawn within 6 weeks	Methylprednisolone 1 g/day×3 days, followed by oral prednisone 1 mg/kg, tapered and withdrawn within 9 weeks
Rechallenge	Response to initial treatment with ICI	Partial response	Progressive disease
	Time from first ICI treatment to ICI rechallenge	7 months	8 months
	ICI	Avelumab 10 mg/kg/2 weeks, 20 infusions	Pembrolizumab 2 mg/kg/3 weeks, 2 infusions
	Associated treatment	Prednisone 20 mg/day, tapered and withdrawn within 3 months	–
	irAE	None	None
	ICI-myositis	No recurrence of myositis with no symptoms, normal CK level, normal electromyography and absence of muscle hypermetabolism on TEP	No recurrence of myositis without any symptoms, normal CK level
	Tumour response	Ongoing partial response after 9 months	Death due to progressive disease at week 6

CK, creatine kinase; FDG-PET, fluorodeoxyglucose-positron emission tomography; HLA, human leucocyte antigen; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; ULN, upper limit normal.

Neither myositis-specific nor myasthenia gravis autoantibodies were detected. ICIs were stopped and three pulses of methylprednisolone followed by tapering doses of prednisone were given leading to complete remission within 8 weeks. Because of the lack of efficacy of the single infusion of ICI combination followed by three infusions of dacarbazine, pembrolizumab was introduced 8 months after the myositis episode. The patient presented no irAEs or myositis (table 1) but died due to melanoma progression.

Despite the risk of recurrent irAEs, rechallenging ICIs after discontinuation due to previous irAEs remains critical, when considering their potential benefits in terms of survival.[5] These two cases suggest that resuming ICIs can be safe in patients displaying persistent remission of ICI-related myositis.

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