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Immune-Related Myositis and Myasthenia Gravis Overlap Following Pembrolizumab Administration: Case Report and Literature Review

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Abstract

Musculoskeletal immune-related adverse events (irAEs), including immune-related myositis (irMyositis), are increasingly being recognized following immune checkpoint inhibitor (ICI) therapy. This is a case of irMyositis overlap with immune-related myasthenia gravis (irMG) following pembrolizumab administration for non-small cell lung cancer. A 73-year-old woman presented to the rheumatologist with dyspnea, fatigue, proximal muscle weakness, diplopia, and eyelid weakness. Creatine kinase (CK) and aldolase were elevated, and electrodiagnostic studies revealed muscle inflammation and necrosis, with decremental response on repetitive nerve stimulation and evidence of postsynaptic neuromuscular junction dysfunction. Improvement of symptoms and normalization of CK occurred after initiation of prednisone and pyridostigmine, but ultimately cancer progressed and the patient died. Prompt initiation of corticosteroids with or without pyridostigmine for irMyositis-irMG overlap can produce clinical improvement in many patients, but further studies are needed to corroborate previous case series showing successful re-challenge with ICI in such cases.

***Keywords:** immune checkpoint inhibitors, immune-related adverse events, immune-related myositis, immune-related myasthenia gravis.*

Key messages

- irMyositis can overlap with irMG and ICI-induced myocarditis, which distinguishes it from the usual presentation of IIM, and often has negative myositis specific antibodies but positive acetylcholine receptor antibodies.
- Treatment consists of prompt discontinuation of ICI followed by corticosteroids and pyridostigmine in the case of overlap with irMG.
- There have been cases reported of successful re-challenge with ICI following resolution of symptoms and normalization of laboratory parameters such as CK, but this remains controversial.

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of various solid organ and hematologic tumors, including melanoma, lung cancer, triple-negative breast cancer, urothelial and renal cell carcinoma, hepatocellular carcinoma, and other malignancies [1]. Currently FDA-approved monoclonal antibody agents inhibit two targets in the immune checkpoint inhibition pathway: cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) [2]. The CTLA-4 inhibitor, ipilimumab, and the PD-1 inhibitors pembrolizumab and nivolumab were the first FDA-approved drugs followed by the PD-L1 inhibitors atezolizumab and durvalumab [3]. ICIs modulate molecular pathways utilized by cancer cells to evade recognition by the immune system; therefore, inhibition of checkpoint

pathways can bolster the antitumor activity of the immune system [4].

Although removing checkpoint inhibition against the immune system improves the antitumor response, ICIs have been associated with autoimmune inflammatory reactions, known as immune-related adverse events (irAEs) [5]. These result from a diminished natural check on the immune system leading to an increased tendency toward autoimmunity, whether by CTLA-4 in its inhibition of the early T cell response, or PD-1 and PD-L1 in their modulation of peripheral T cells [5]. The most common irAEs occur in the GI tract (colitis), endocrine system (hypo- and hyperthyroidism), liver (transaminitis), skin (rash, vitiligo), lungs (pneumonitis), and musculoskeletal system (arthralgia/arthritis, myositis). Neurologic, cardiovascular, and renal irAEs are less common, and have presented as neuromuscular disease, polyneuropathy, myocarditis, and nephritis [6]. ICI-induced myositis in particular can present in an overlap syndrome with neuromuscular autoimmune disease [7]. We describe here a case of immune-related myositis (irMyositis) with myasthenia gravis (irMG) overlap in a patient receiving ICI treatment for non-small cell lung cancer.

Case Description

A 73-year-old woman with lung adenocarcinoma presented to rheumatology with several months of fatigue, generalized weakness, exercise intolerance and dyspnea. Functionally, she had difficulty getting up from a chair and using a hair dryer, and complained of late-day diplopia, hoarseness, and drooping eyelids when tired. She denied dysphagia, rash, arthralgia, or Raynaud phenomenon.

Two years prior to presentation stage IIIA T2aN2M0 adenocarcinoma of the right middle lobe of the lung was diagnosed with pleural and angiolymphatic invasion after right middle lobectomy and mediastinal lymph node dissection. Clinical and radiological remission after four cycles of adjuvant carboplatin and pemetrexed were achieved, but the following year she developed horizontal diplopia and a new left sphenoid sinus lesion and L2 vertebral bony metastases were found. She received palliative radiation and three cycles of cisplatin, pemetrexed, and pembrolizumab.

After three cycles of this chemotherapy regimen, the aforementioned symptoms manifested along with elevated serum transaminases and prednisone begun at 60 mg daily with a gradual taper. Muscle weakness persisted with an elevated creatine kinase (CK) of 473 (normal 29-143 U/L). Prednisone taper was restarted just prior to rheumatology visit and the chemotherapy regimen was discontinued after three cycles due to these symptoms.

On presentation to the rheumatology clinic, the patient exhibited 4-/5 strength of the neck flexors and bilateral deltoids and iliopsoas. There were no cranial nerve deficits, sensory or gait disturbances, or arthritis. Numerous vertebral body metastases were found and a chest CT revealed no interstitial lung disease. There was no evidence of cord compression on cervical spine MRI. The aldolase (16.3 U/L; normal <8.1) and LDH (372 U/L; normal 120-250) were elevated and the troponin, acetylcholine receptor binding, blocking, and modulating antibodies, muscle-specific kinase (MuSK) and striated muscle antibodies were all negative. Electrodiagnostic testing revealed an abnormal decremental response to slow repetitive stimulation consistent with a postsynaptic defect in neuromuscular junction transmission. Myopathy was also noted with signs of muscle inflammation or necrosis in the right biceps brachii, without features of a large fiber polyneuropathy.

The diagnosis of irMyositis with irMG overlap was made, and the prednisone taper was continued given the patient's overall clinical improvement. The patient was referred to neurology and started on pyridostigmine with improvement in her diplopia. The trend in the CK and aldolase over the treatment period are given in table 1. The CK normalized and muscle strength improved, but bony metastatic disease progressed; she subsequently died on hospice.

	End of previous prednisone taper	Interim laboratory follow-up	Initial rheumatology clinic visit†	Four weeks following pyridostigmine initiation	Last clinical follow-up
CK (U/L)	473	393	213	70	31
Aldolase (U/L)			16.3	7.3	
†Occurred four days after start of a new prednisone taper starting at 50 mg/day.					

Table 1: Trends in creatine kinase (CK) and aldolase over the clinical course of corticosteroid treatment for immune-related myositis and myasthenia gravis.

Discussion

Our patient had irMyositis in overlap with irMG after pembrolizumab for relapsed metastatic lung adenocarcinoma. Symptoms initially improved on prednisone and pyridostigmine but ultimately bony metastatic disease progressed.

A recent review of ICI-induced neuromuscular disease noted a frequency of irMyositis of 2.6% with nivolumab, 1% with pembrolizumab, and 0.2% with ipilimumab [8]. Phase III trials of combination nivolumab-ipilimumab therapy showed an incidence of 0.95% for irMyositis, with irMyositis, irMG, and peripheral neuropathy alone or in overlap ranging between 16-25% of cases [8]. Another oncology cohort noted that while most subjects presented

with irMG, a subset manifested myositis-myasthenia or myocarditis-myasthenia overlap (37% and 8% respectively) and 2 of 65 patients developed myasthenia/myositis/myocarditis overlap progressing to respiratory failure [9].

irMyositis is reported to have variable phenotypic presentation in the literature. A retrospective analysis of 10 cases noted oculomotor, limb-girdle, and axial muscle weakness with CK elevation and negative anti-acetylcholine receptor and myositis-associated antibodies [10]. Histopathologic findings have been nonspecific, with reports of normal biopsies as well as necrotizing myopathy [7]. A review of the WHO database of irMyositis case reports found that irMyositis portended a worse prognosis and higher mortality rate than idiopathic inflammatory myopathy (IIM), and more often overlaps with irMG and myocarditis [11]. However, diagnosing irMyositis with comorbid irMG can be difficult in the absence of antibody positivity given that isolated ocular irMyositis has also been reported [12].

Another review of 15 irMyositis cases noted classic IIM features in one subset and other clinical features in the remaining patients [13]. The former patients had dermatomyositis-like skin rashes, an exacerbation of ILD, and positivity of myositis-specific antibodies (MSA), while the remaining atypical cases had myocardial, oculomotor and respiratory muscle/diaphragmatic involvement as well as neuromuscular junction disease. The latter patients had no MSA and positivity of anti-acetylcholine receptor antibodies. Another melanoma case series of immune-related neuromuscular disease noted several patients positive for MSA, including anti-TIF1γ, anti-SRP, and anti-PL7 [14]. Comments on this report posited that the MSA positivity indicated either unmasking of underlying autoimmunity or paraneoplastic disease rather than true irAEs [5,15]. Therefore, MSA detection may provide clues to the underlying pathophysiology of ICI toxicities indicating unmasked autoimmune disease requiring immunosuppressive therapy after ICI treatment, or a paraneoplastic disease process requiring that ICI therapy not be interrupted [15]. A systematic review of the PubMed database of reported cases of irMyositis are provided as a supplement to this article.

ICI efficacy has been correlated with the development of irAEs: a recent review of several retrospective and prospective studies found that in non-small cell lung cancer (NSCLC) in particular, irAE development in patients on anti-PD-1 and anti-PD-L1 therapy correlated with increased progression-free survival, disease control rate, and overall response rate [16]. Additionally, thyroiditis portended a better prognosis compared to other irAEs. With regards to anti-CTLA-4 therapy, the results are conflicting, with some retrospective analyses finding a more favorable response to ICI therapy in patients developing irAEs and others reporting no difference [16]. Furthermore, it is unclear whether the treatment of irAEs with glucocorticoids reduces ICI efficacy, though it has been reported that anti-PD-1 and anti-PD-L1 therapy is less effective for NSCLC in patients treated with glucocorticoids at the start of ICI treatment [16].

The American Society of Clinical Oncology (ASCO) practice guideline describes both the classification and treatment of irAEs of various organ systems according to grades 1–4, increasing in severity [17]. Grade 1 irMyositis can be managed with analgesics and corticosteroids. Grade 2 and above warrant interruption of ICI and may lead to hospitalization with administration of IV corticosteroids, and in some cases IVIg, plasmapheresis, and disease-modifying antirheumatic drugs such as rituximab. In contrast all grades of irMG, due to the potential for rapid clinical deterioration, may require hospital admission in the intensive care unit, and treatment is generally corticosteroids, pyridostigmine, and in some cases IVIg or plasmapheresis. ICI re-challenge is generally not recommended for severe cases of both irMyositis and irMG, although cases of successful reinitation of ICI have been reported [9,18].

Conclusion

Immune-related neuromuscular disease is an increasingly recognized adverse event of ICI therapy. irMyositis varies in presentation but usually differs from IIM in its more frequent overlap with irMG, ocular and bulbar involvement, and negativity of MSA. irMyositis can also overlap with myocarditis, which is associated with a worse clinical course. Successful re-challenge of ICI therapy has been reported in irMyositis and irMG following appropriate glucocorticoid and immunosuppressive therapy.

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Conflicts of interest/disclosures
The authors have declared no conflicts of interest relevant to this article.

Data Availability
The data underlying this article are included within the article.

Supplementary Material
A systematic PubMed database search was conducted to review immune-related case reports and series published as of October 27, 2020 and a table was constructed, which is included as supplementary material.

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Supplemental table: PubMed database search of immune-related myositis case reports and series

A Pubmed search was performed on October 27, 2020 using the search term "immune-checkpoint inhibitor myositis OR immune-checkpoint inhibitor induced myositis OR immune-related myositis OR immune checkpoint myositis". Of these search results, English-language case reports and series of immune-related myositis (irMyositis) were reviewed and the following table constructed. Cases of irMyositis cited within the referenced reports were listed in the table separately. Reports of immune-related myasthenia gravis (irMG) and immune-related myocarditis were included if there was overlap with irMyositis. Papers without sufficient detail to complete the table were excluded.

Abbreviations/definitions: CK=creatine kinase, pulsed methylprednisolone=1g intravenous methylprednisolone x 3-5 days, IVIg = intravenous immunoglobulin, MTX = methotrexate, MMF = mycophenolate mofetil, TNFi = tumor necrosis factor inhibitor, RTX = rituximab, AZA = azathioprine.

Author	Year	# cases	Associated ICI (frequency)	Treatment (%)	Outcomes (%)
Kobayashi M et al [1]	2020	1	durvalumab	Oral corticosteroid	Resolution
Wong et al [2]	2020	4	Nivolumab + ipilimumab 2/4 (50%), nivolumab 1/4 (25%), pembrolizumab 1/4 (25%)	Pulsed methylprednisolone 2/4 (50%) Pyridostigmine 3/4 (75%) Oral corticosteroid 3/4 (75%) IVIg 3/4 (75%) No treatment 1/4 (25%)	Resolution (100%)
Uchio et al [3]	2020	1	pembrolizumab	ICI discontinuation without immunosuppression	Improvement in CK, subsequently disease progression and death
Matsui et al [4]	2020	1	pembrolizumab	IV corticosteroid and plasma exchange, followed by pulsed methylprednisolone	Critical illness and death
Okubo et al [5]	2020	1	Nivolumab + ipilimumab	Oral corticosteroids and change to nivolumab monotherapy	Resolution
Jeyakumar et al [6]	2020	1	cemiplimab	Pulsed methylprednisolone, plasma exchange, IVIg	Critical illness and death
Roberts et al [7]	2020	9	Not specific	Prednisone (100%) MTX 2/9 (22%) MMF 2/9 (22%) TNFi 1/9 (11%) RTX 1/9 (11%)	Noted complete resolution in 4/9 (44%), partial resolution in 4/9 (44%)
Veccia et al [8]	2020	1	nivolumab	IV followed by oral corticosteroid, IVIg, pyridostigmine	Critical illness and death
Kimura et al [9]	2016	1	nivolumab	Pulsed methylprednisolone, then oral corticosteroid, plasma exchange and immunoadsorption, IVIg, pyridostigmine	Clinical improvement
Chen JH et al [10]	2017	1	Nivolumab + ipilimumab	IV corticosteroids, then oral corticosteroids and pyridostigmine	Clinical improvement
Liao et al [11]	2014	1	ipilimumab	IV corticosteroids, plasmapheresis, IVIg, pyridostigmine	Clinical improvement
Calvo et al [12]	2015	1	nivolumab	Corticosteroids, IVIg	Clinical deterioration and death
Maeda et al [13]	2016	1	nivolumab	Concurrent corticosteroids	Resolution
Shirai et al [14]	2016	1	nivolumab	IV corticosteroids	Clinical deterioration and death
Chang et al [15]	2017	1	nivolumab	Pyridostigmine, IVIg	Clinical improvement, subsequently hospice and death
Chen YH et al [16]	2017	1	nivolumab	IV corticosteroids, pyridostigmine	Respiratory failure and death
Tan et al [17]	2017	1	nivolumab	Pulsed methylprednisolone, IVIg, pyridostigmine	Critical illness, subsequent resolution
Suzuki et al [18]	2017	4	nivolumab	Immunosuppressive therapy	Unclear from abstract

Hibino et al [19]	2018	1	pembrolizumab	Pyridostigmine, oral corticosteroids	Resolution
Kang et al [20]	2018	1	nivolumab	IV then oral corticosteroids, plasmapheresis, pyridostigmine	Improvement, discharge to rehab (subsequent death)
Sutaria et al [21]	2019	1	Nivolumab + ipilimumab	Pulsed methylprednisolone, IVIg, subsequently oral corticosteroids	Resolution
Mohn et al [22]	2019	2	Nivolumab	Pulsed methylprednisolone 1/2 (50%), IVIg 1/2 (50%), IV corticosteroids 1/2 (50%)	Improvement but subsequent death from GI bleed 1/2 (50%), sudden in-hospital death of unknown cause 1/2 (50%)
Fuentes-Antras et al [23]	2020	1	pembrolizumab	Pulsed methylprednisolone, pyridostigmine, IVIg, infliximab	Critical illness and death
von Itzstein et al [24]	2020	1	durvalumab	IV corticosteroids, IVIg, then oral corticosteroid taper	Resolution
Seki M et al [25]	2019	19	Nivolumab 11/19 (58%), Pembrolizumab 8/19 (42%)	No treatment (2/19), Pulsed methylprednisolone 9/19 (47%), Oral corticosteroid 17/19 (89%), IVIg 3/19 (16%) Tacrolimus 1/19 (5.3%)	Clinical improvement 18/19 (95%%), Death 7/19 (37%)
Lie et al [26]	2020	1	nivolumab	Pulsed methylprednisolone, oral corticosteroid taper, MMF	Clinical improvement
Ohira et al [27]	2020	1	Nivolumab + ipilimumab	Pulsed methylprednisolone, plasma exchange, IVIg, MMF, oral corticosteroids	Critical illness, development of multiple other irAEs (colitis, oral mucositis), subsequent improvement
Mathews & Romito [28]	2020	1	Nivolumab + ipilimumab	High dose corticosteroids, plasma exchange, pyridostigmine	Critical illness, death
Hayakawa et al [29]	2020	1	pembrolizumab	Pulsed methylprednisolone	Clinical improvement
Xing Q et al [30]	2020	1	sintilimab	IV corticosteroids, IVIg, pyridostigmine, plasma exchange	Critical illness, subsequent tracheostomy and remains ventilator-dependent
Garibaldi et al [31]	2020	1	pembrolizumab	corticosteroids	Resolution
Vermeulen et al [32]	2020	3	Ipilimumab 1/3 (33%), Nivolumab 1/3 (33%), Atezolizumab 1/3 (33%)	IV corticosteroids 3/3 (100%), Plasma exchange 2/3 (67%), Pyridostigmine 2/3 (67%), Cyclosporine 1/3 (33%)	Death 1/3 (33%), Clinical improvement 2/3 (67%),
Luecke E et al [33]	2020	1	pembrolizumab	Glucocorticoids, plasmapheresis, pyridostigmine	Critical illness and death
Ozarczuk et al [34]	2020	1	Nivolumab + ipilimumab	Oral corticosteroids, pyridostigmine, IVIg	Resolution

Nakanishi et al [35]	2019	1	nivolumab	corticosteroids	Clinical deterioration and death
Liu Y et al [36]	2019	1	Nivolumab + ipilimumab	Pulsed methylprednisolone	Resolution (subsequent death due to progression)
Safa et al [37]	2019	63 (24 patients with concurrent myositis)	PD-1 blockade (82%)	Corticosteroids 59/63 (94%), acetylcholinesterase inhibitors 32/63 (51%), IVIg 30/63 (48%), plasmapheresis 28/63 (44%), immunosuppression 10/63 (16%)	Resolution 12/63 (19%), invasive ventilation 12/63 (19%)
Valenti-Azcarate [38]	2020	1	Nivolumab + ipilimumab	IV corticosteroids	Resolution
Todo et al [39]	2019	1	pembrolizumab	Corticosteroids	Resolution
Sekiguchi et al [40]	2019	1	pembrolizumab	Pulsed methylprednisolone, IVIg, oral corticosteroids	Improvement
Kamo et al [41]	2019	2	Pembrolizumab 2/2 (100%)	IV corticosteroids 2/2 (100%), plasma exchange 1/2 (50%)	Improvement 2/2 (100%)
Konstantina et al [42]	2019	1	Pembrolizumab	Corticosteroids, pyridostigmine, IVIg, rituximab	Critical illness and death
Khoo et al [43]	2019	1	atezolizumab	Pulsed methylprednisolone	Improvement
Saibil et al [44]	2019	1	Nivolumab + ipilimumab	Pulsed methylprednisolone, IVIg, infliximab	Critical illness and death
Fazel and Jedlowski [45]	2019	1	Nivolumab + ipilimumab	IV corticosteroids followed by pulsed methylprednisolone and IVIg, plasmapheresis	Death
Charles J et al [46]	2019	1	nivolumab	IV corticosteroids, IVIg, MMF	Death
Kadota et al [47]	2019	15	Pembrolizumab 3/15 (20%), nivolumab 5/15 (33%), ipilimumab 4/15 (27%), nivolumab + ipilimumab 3/15 (20%)	Corticosteroids 15/15 (100%), IVIg 6/15 (40%), plasmapheresis 6/15 (40%), infliximab 2/15 (13%)	Death 7/15 (47%), improvement 8/15 (53%)
Kobayashi T et al [48]	2019	1	nivolumab	Pulsed methylprednisolone	Resolution
Monge et al [49]	2018	1	nivolumab	corticosteroids	Resolution
Marano et al [50]	2019	1	nivolumab	Oral corticosteroids, IVIg	Clinical improvement
Puwanant et al [51]	2019	22	Ipilimumab 5/22 (23%), nivolumab 3/22 (14%), pembrolizumab 9/22 (41%), nivolumab + ipilimumab 2/22 (9%), tremelimumab + durvalumab 2/22 (9%), ipilimumab + pembrolizumab 1/22 (5%)	Corticosteroids, IVIg, plasma exchange, MMF, tacrolimus, infliximab (percentages given for entire cohort, not myositis subgroup)	Improvement 12/22 (55%), death 6/22 (27%)
Reynolds and Guidon [52]	2019	1	Pembrolizumab + ipilimumab	Pulsed methylprednisolone, oral corticosteroids	Resolution
Rota et al [53]	2018	2	nivolumab	Pulsed methylprednisolone, IVIg 2/2 (100%)	Resolution 1/2 (50%), death ½ (50%)
Tauber et al [54]	2019	1	Nivolumab + ipilimumab	IV followed by oral corticosteroids, IVIg	Resolution

Moreira et al [55]	2019	20	Nivolumab 2/20 (10%), pembrolizumab 12/20 (60%), ipilimumab 1/20 (5%), nivolumab + ipilimumab 5/20 (25%)	Corticosteroids 16/20 (80%), pyridostigmine 1/20 (5%), IVIg 4/20 (20%), no treatment 4/20 (20%)	Resolution 11/20 (55%), death 3/20 (15%), sequelae 4/20 (20%), improvement 2/20 (10%)
Mitchell et al [56]	2018	3	Nivolumab 2/3 (67%), pembrolizumab 1/3 (33%)	No treatment 1/3 (33%), corticosteroids 2/3 (67%), AZA 1/3 (33%), MMF 1/3 (33%)	Improvement 2/3 (67%), resolution 1/3 (33%)
Imai et al [57]	2019	1	Pembrolizumab	Pulsed methylprednisolone, IVIg, tacrolimus	Critical illness, death
Roberts JH et al [58]	2018	2	Nivolumab + ipilimumab 2/2 (100%)	Oral corticosteroids 2/2 (100%), IV corticosteroids 1/2 (50%), MTX 2/2 (100%)	Improvement
Delyon et al [59]	2019	2	Avelumab 1/2 (50%), Nivolumab + ipilimumab 1/2 (50%)	Pulsed methylprednisolone 1/2 (50%), oral corticosteroids 2/2 (100%)	Resolution 2/2 (100%)
Anquetil et al [60]	2018	180	Nivolumab 92/180 (51%), pembrolizumab 34/180 (19%), durvalumab 20/180 (11%), atezolizumab 1/180 (0.6%), avelumab 2/180 (1.1%)	Not reported	Fatality 36/170 (21%)
Narvaez et al [61]	2018	2	Avelumab 1/2 (50%), pembrolizumab 1/2 (50%)	NSAIDS 2/2 (100%), colchicine 1/2 (50%)	Resolution 1/2 (50%), death 1/2 (50%)
Touat et al [62]	2018	10	Nivolumab 6/10 (60%), pembrolizumab 1/10 (10%), durvalumab 1/10 (10%), nivolumab + ipilimumab 2/10 (20%)	Immunosuppression 9/10 (90%)	Clinical improvement 10/10 (100%)
Mahmood et al [63]	2018	1	Durvalumab + treme limumab	Pulsed methylprednisolone, MMF	Clinical improvement
Shah et al [64]	2019	6	Ipilimumab 1/6 (17%), pembrolizumab 1/6 (17%), atezolizumab 1/6 (17%), nivolumab + ipilimumab 3/6 (50%)	IV corticosteroids 2/6 (33%), oral corticosteroids 3/6 (50%), infliximab 1/6 (17%), plasmapheresis 3/6 (50%), IVIg 2/6 (33%), pyridostigmine 1/6 (17%), NSAIDs 1/6 (17%)	Death 2/6 (33%), improvement 4/6 (67%)
Liewluck et al [65]	2018	5	Pembrolizumab 5/5 (100%)	IV corticosteroids 2/5 (40%), oral corticosteroids 5/5 (100%), plasma exchange 3/5 (60%)	Death 2/5 (40%), improvement 3/5 (60%)
Kudo et al [66]	2018	1	nivolumab	Corticosteroids	Death
Badvinac et al [67]	2018	1	nivolumab	corticosteroids	Improvement
Bourgeois-Vionnet et al [68]	2018	1	nivolumab	Oral corticosteroids, IVIg	Improvement
Martini et al [69]	2018	2	Anti-PD-L1 combination therapy 1/2 (50%), anti-PD-1 monotherapy 1/2 (50%)	Corticosteroids 2/2 (100%), IVIg and infliximab 1/2 (50%)	Improvement 1/2 (50%), ongoing toxicity 1/2 (50%)
Pushkarevskaya et al [70]	2017	2	ipilimumab	IV corticosteroids 2/2 (100%), MMF 2/2 (100%), IVIg 1/2 (50%)	Resolution 2/2 (100%)
Ogawa et al [71]	2017	1	nivolumab	Corticosteroids and azathioprine	Death
John S et al [72]	2017	1	Tremelimumab + durvalumab	Corticosteroids, IVIg, plasma exchange, pyridostigmine	Death

Diamantopoulos et al [73]	2017	1	pembrolizumab	Corticosteroids, IVIg, plasmapheresis	Death
Behling et al [74]	2017	1	nivolumab	IV corticosteroids, temporary pacemaker	Critical illness and death
Calabrese et al [75]	2017	1	Tremelimumab + durvalumab	IV corticosteroids	Improvement
Johnson DB et al [76]	2016	2	Nivolumab + ipilimumab	IV corticosteroids 1/2 (50%), pulsed methylprednisolone 1/2 (50%), infliximab 1/2 (50%)	Death 2/2 (100%)
Graff et al [77]	2016	1	pembrolizumab	corticosteroids	Resolution
Sheik Ali et al [78]	2015	1	ipilimumab	IV and oral corticosteroids	Resolution

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