Chronic inflammatory demyelinating polyradiculopathy as a paraneoplastic manifestation of metastatic melanoma

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Introduction

Chronic inflammatory demyelinating polyradiculopathy (CIDP) is an acquired autoimmune neuropathy typically characterized by progressive diffuse limb weakness, sensory loss and hyporeflexia with a disease course of 2 months or greater. The underlying pathology is usually due to increased inflammatory T-cell and macrophage activity. It typically follows a relapsing course with many patients requiring regularly scheduled immunotherapy such as corticosteroids and/or immunoglobulins [1]. Many cases are sporadic without an underlying causative or associated disease process. However, there have been multiple reports that suggest an association with malignancy. The most common associations are hematologic malignancies such as lymphoma and leukemia [2]. Solid tumor malignancies are also known to be implicated. There have been several reported cases and series evaluating the association between CIDP with melanoma [2-10]. Despite the increasing number of reports over the years, this association is still not widely known, which can lead to diagnostic delay. In this article, we report a case of a patient with a known remote history of resected early-stage cutaneous melanoma, who presented with severe refractory CIDP. During his diagnostic evaluation, he was found to have recurrent metastatic malignant melanoma. Treatment of both diseases resulted in marked, sustained clinical improvement. This case highlights the importance of the identification and treatment of melanoma in CIDP patients.

Case

A 50-year-old male with a remote history of resected cutaneous melanoma that was removed 6 years prior presented with weakness of all limbs and associated back and neck pain. His initial examination demonstrated predominantly proximal upper and lower extremity weakness with intact sensation and reflexes. Magnetic resonance imaging (MRI) of his brain and cervical spine were unrevealing. Initial nerve conduction studies at 2 months demonstrated normal sural and median sensory responses, normal median compound muscle action potential (CMAP) with a normal F-wave latency and reduced peroneal motor CMAP recording at the extensor digitorum brevis. Electromyography (EMG) examination showed the presence of long duration motor unit potentials with neurogenic recruitment pattern in the C5-8 and L3-4 nerve root innervated muscles without active denervation. Electrodiagnosis at that time was thought to be most consistent with cervical (C5-8) and lumbar (L3-4) radiculopathies. Physical therapy was recommended.

His weakness progressed to the point that he could not ambulate, and he was hospitalized 10 days after the initial EMG. Examination showed proximal and distal upper and lower extremity weakness bilaterally but intact reflexes and sensation. MRI of the lumbar spine with contrast showed the presence of nerve root enhancement of the cauda equina. Cerebrospinal fluid (CSF) testing revealed the following: protein of 128 mg/dL, glucose of 76 mg/dL and 1 nucleated cell/μL. Cytology was negative for malignant cells. He was treated with a course of intravenous immunoglobulin (IVIG) at 2.0 grams per kilogram of body weight for a presumed diagnosis of CIDP, which led to significant improvement and regaining independent ambulation.

Approximately 1 month later, he was readmitted to the hospital and was found to have significant proximal arm and leg weakness again. Another course of IVIG was given, which led to improvement, and he was also started on prednisone of 30 mg daily. Repeat electrodiagnostic testing after that hospitalization (approximately 6 weeks from the initial electrodiagnostic study) re-demonstrated absent peroneal motor response at the extensor digitorum brevis but also showed interval prolongation of the median motor response latency. Additional motor nerve conduction studies of the ulnar nerve revealed the presence of a partial conduction block, temporal dispersion, reduced conduction velocity and a prolonged F wave latency. Needle electrode examination showed more widespread and a more significant presence of long duration motor unit potentials with neurogenic recruitment in the left C5-T1 and L3-S1 nerve root innervated muscles without active denervation—indicating a worsening polyradiculopathy. He relapsed again approximately 6 weeks later and received 5 sessions of plasmapheresis. Plasmapheresis led to quick improvement, and prednisone was increased to 60mg daily. Hhowever, his weakness relapsed 1 week later which led to readmission. Repeat MRI of the spine revealed the presence of contrast enhancement of thoracic and lumbosacral nerve roots. Repeat CSF testing revealed the following: protein of 196 mg/dL, glucose of 110 mg/dL and 1 nucleated cell/μL with negative cytology. A whole-body positron emission tomography (PET) scan showed multiple hypermetabolic lymph nodes in the right axilla. Further excisional biopsy of the lymph nodes revealed the presence of BRAF

positive metastatic melanoma. He was subsequently treated with complete surgical resection, adjuvant local radiation therapy, encorafenib and binimetinib. For his refractory CIDP, he was treated with 2 doses of rituximab at 1000mg each, mycophenolate mofetil and maintenance plasmapheresis once every 2 weeks for a total of 4 months. This combinatorial treatment of melanoma and CIDP led to significant and persistent improvement of his muscle strength. Repeat electrodiagnostic testing performed 3 months after his last hospitalization (6 months from the second electrodiagnostic study) showed recovery of median and ulnar F responses as well as improvement in motor response amplitudes, latencies and conduction velocities. Repeat PET scan revealed a reduction of hypermetabolic activity in the right axilla without identification of additional hypermetabolic foci. At his last evaluation (1 year from the initial onset), his physical examination showed normal muscle strength, intact deep tendon reflexes and normal sensation while on oral mycophenolate mofetil for CIDP and continuing targeted chemotherapy (encorafenib and binimetinib) for melanoma.

Discussion

This case highlights the importance of the awareness of the association of melanoma with CIDP. A proposed pathologic mechanism for this association is molecular mimicry due to similar surface antigens on melanocytes and peripheral nerves [4].

Table 1 provides a summary of this patient and other reported cases of polyneuropathy associated with melanoma to date. CIDP has also been reported as a complication of immunotherapy for melanoma [11, 12]. Because it is difficult to distinguish whether the neuropathy was secondary to melanoma or a complication of treatment, these cases are not included in the table.

Comparing the characteristics of these cases highlights certain pitfalls in identifying melanoma in CIDP patients. Despite the increasing number of case reports in the literature, this association is still not widely known. Identification of melanoma can be challenging for the neurologist as typical melanoma skin findings may not be present at the time of CIDP and patients with melanoma may rarely report constitutional symptoms. The diagnosis of melanoma in these cases required extensive imaging and verification via biopsy. Testing for malignancy through serum markers, computed tomography, and PET scans are also not standard components in the evaluation of CIDP [1]. Lastly, there is wide variability in the delay between the development of melanoma and the onset of neuropathy. At times, the interval could be many years.

Our patient's clinical course suggests that clinical improvement for these patients relies on treating both the neuropathy and underlying malignancy. His initial course relapsed frequently despite the use of corticosteroids, IVIG and PLEX prior to the recognition of underlying melanoma. These treatment modalities resulted in quick but non-sustained clinical improvement prior to the initiation of anti-melanoma therapy. Sustained clinical improvement occurred when he was receiving treatment for both CIDP and melanoma. This rationale is congruent with the proposed mechanism of molecular mimicry between these 2 entities. Our case highlights the need for recognizing that CIDP can be a paraneoplastic manifestation of melanoma and the importance of treating such patients with combined therapies to achieve an optimal outcome.

Table 1. A list of published cases describing CIDP in association with melanoma

Reference	Age	Sex	Time of melanoma diagnosis before or after CIDP onset	Clinical features	EMG features	Melanoma site	CIDP treatment	Melanoma treatment
Bird et al. [3]	62	M	4 months after	Ascending paresthesias, proximal>distal limb weakness, areflexia	Demyelinating	Axillary lymph node	Plasmapheresis, prednisone	Resection
Bird et al. [3]	43	M	6 months after	Ascending numbness, distal limb weakness, areflexia	Demyelinating	Axillary lymph node	Prednisone	Resection
Bird et al. [3]	49	M	12 months before	Intermittent distal lower extremity paresthesias and weakness, areflexia	Demyelinating	Skin	Declined treatment	Radiation
Weiss et al. [4]	73	F	3 years before	Ascending paresthesias, proximal limb weakness, areflexia	Demyelinating	Not stated	Not stated	Not stated
Antoine et al. [5]	64	M	10 years after	Paresthesias and weakness, diffuse hyporeflexia	Demyelinating	Not stated	Not stated	Not stated
Kloos et al. [6]	68	F	17 years before (skin) 3 months before (lymphadenopathy)	Diplopia, proximal weakness, hyporeflexia	Axonal	Iliac lymph node	IVIG, dexamethasone, plasmapheresis for 1 relapse	Immunotherapy clinical trial
Rousseau et al. [7]	32	M	5 months before	Proximal limb weakness, distal lower extremity areflexia	Demyelinating	Skin	IVIG	Resection
Palma et al. [8]	66	M	14 months before	Proximal limb weakness and areflexia	Demyelinating	Lung	IVIG	Chemotherapy
Dbouk et al. [9]	52	M	6 years before (skin) 3 years before (liver metastasis)	Distal paresthesias, proximal limb and facial weakness, dyspnea	Demyelinating	Skin, liver	Plasmapheresis, prednisone	1st: Resection, chemotherapy 2nd: Chemotherapy
Dbouk et al. [9]	58	F	Concurrent	Distal paresthesias, gait impairment	Demyelinating	Para-aortic lymph node	Plasmapheresis, prednisone	Chemotherapy
Chau et al. [10]	67	M	1 month before	Distal paresthesias, Proximal limb weakness, diffuse hyporeflexia	Demyelinating	Skin, axillary lymph node, spleen	IVIG, intravenous methylpredniso-lone	Not stated
Present case	50	M	6 years before	Back pain, proximal limb weakness	Demyelinating	Axillary lymph node	IVIG, plasmapheresis, prednisone	Chemotherapy, radiation

Abbreviations: CIDP: chronic inflammatory demyelinating polyradiculopathy; EMG: electromyography and nerve conduction study; IVIG: intravenous immunoglobulin

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