

A case of paraneoplastic myelopathy associated with the neuromyelitis optica antibody

Sabine Mueller, Dena B Dubal and S Andrew Josephson*

SUMMARY

Background A 63-year-old woman with a history of metastatic breast cancer presented to the emergency department with chest pain in a band-like distribution. Within 1 day of presentation the patient developed bilateral lower-extremity weakness and urinary retention. The emergence of these symptoms coincided with the recurrence of her metastatic breast cancer. Fifteen months before presentation the patient had experienced a similar episode of myelopathy in the setting of recurrence of her breast cancer, from which she recovered completely following treatment with steroids.

Investigations General and neurological examination, routine laboratory testing, MRI of the brain and spine, tests for serum autoimmune antibodies, infectious serology testing, lumbar puncture, paraneoplastic panel, neuromyelitis optica antibody testing, evaluation for celiac disease, CT scans of the chest, abdomen and pelvis, whole-body [¹⁸F]fluoro-2-deoxyglucose PET scan, lymph node biopsy, electroencephalography observing visual and brainstem auditory evoked potentials, and neuro-ophthalmological examination.

Diagnosis Myelopathy, possibly paraneoplastic, associated with the neuromyelitis optica antibody in the setting of metastatic breast cancer.

Management Corticosteroids to treat the myelopathy and chemotherapy for the breast cancer.

KEYWORDS aquaporin 4, breast cancer, neuromyelitis optica antibody, paraneoplastic myelopathy, transverse myelitis

CME

Vanderbilt Continuing Medical Education online

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

Competing Interests

The authors declared no competing interests.

THE CASE

A 63-year-old woman with a history of metastatic breast cancer, and with possible celiac disease, presented to the emergency department with sudden-onset chest pain in a band-like distribution. Evaluation by the cardiology service ruled out myocardial infarction. Over the next 24 hours, the patient developed weakness and numbness in both legs, and urinary retention. A neurology consultation was obtained and the patient was diagnosed with an acute spinal cord process. On examination, the patient was in no acute distress. Her general examination was notable for alopecia secondary to chemotherapy and unilateral mastectomy, which she underwent after being diagnosed with breast cancer 2 years earlier. The patient had normal rectal tone. On neurological examination, the patient was fully alert and oriented. Results of cranial nerve examination were normal, motor examination revealed flaccid tone and moderate pyramidal weakness in both legs, and sensory examination showed a sensory level to pinprick at T4–T6 and to vibration at C3–C4. Proprioception was decreased bilaterally at the toes and Romberg's sign was not present. The patient was areflexic and had been in an areflexic state since her first course of chemotherapy 2 years earlier. The patient demonstrated extensor plantar responses bilaterally.

The patient had experienced a similar episode of myelopathy 15 months previously, which had started with headache, paresthesias and leg and arm weakness (the weakness was greater in her arms). At the time, she was evaluated at a different institution and diagnosed with probable paraneoplastic myelopathy in the setting of recurrent breast cancer. The patient had received

S Mueller is a Pediatric Neurology Fellow, DB Dubal is a Clinical Fellow and SA Josephson is a Clinical Assistant Professor in the Department of Neurology, University of California San Francisco, San Francisco. DB Dubal is also a Postdoctoral Fellow at the Gladstone Institute, San Francisco, CA, USA.

Correspondence

*Department of Neurology, University of California San Francisco, 505 Parnassus Ave, Box 0114, San Francisco, CA 94143, USA
ajosephson@memory.ucsf.edu

Received 21 August 2007 Accepted 18 January 2008 Published online 4 March 2008

www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0765

a 5-day course of 1 g/day intravenous methylprednisolone sodium succinate followed by a 6-week dexamethasone taper, as well as weekly doses of paclitaxel and bevacizumab to treat her breast cancer. She made a full clinical recovery, and no residual disease was reported on repeat spinal MRI 4 months following the onset of that episode.

During this presentation the patient underwent an extensive laboratory evaluation for infectious, autoimmune, celiac-related and metabolic conditions (Table 1). Most notably, tests for the neuromyelitis optica (NMO) antibody were positive. Tests for antibodies to double-stranded DNA and to extractable nuclear antigens were not performed. MRI of the spine demonstrated signal abnormality, and spinal cord expansion from C5 to T10, on T2-weighted images (Figure 1A). Patchy enhancement was noted from T6 to T9. There was no sign of spinal cord compression. Brain MRI did not reveal any demyelinating or white matter lesions, but demonstrated small metastases in the cerebellum and right hemisphere. Whole-body PET scan showed multiple areas of increased [^{18}F]fluoro-2-deoxyglucose uptake, including in both lung fields and in the mediastinum, liver and cerebellum. The lower thoracic region of the spine showed possible increased activity, but was otherwise negative for [^{18}F]fluoro-2-deoxyglucose uptake. CT scans of the chest, abdomen and pelvis revealed mediastinal and hilar lymphadenopathy and multiple pulmonary nodules. A lymph node biopsy confirmed the diagnosis of metastatic breast cancer.

The patient was treated for myelopathy with a 5-day course of 1 g/day intravenous methylprednisolone sodium succinate, which immediately led to improved strength and sensation. She was started on capecitabine for her breast cancer and underwent gamma knife surgery for the brain metastases. The patient was discharged on oral prednisone 60 mg/day, which was slowly tapered by 10 mg per week, and on oral capecitabine 2,000 mg every morning and 1,500 mg every evening for 14 days. Her symptoms improved rapidly following treatment with corticosteroids. During a follow-up visit 1 month later, the patient was able to walk independently and had regained vibratory sensation to the knees. She no longer experienced urinary retention. Repeat spinal MRI at this time showed marked improvement, revealing only mild residual

linear T2 signal abnormality and no evidence of enhancement (Figure 1B). On the basis of the positive test result for the NMO antibody, the patient underwent a neuro-ophthalmological examination and electroencephalography observing brainstem auditory-evoked and visual-evoked potentials, the results of which were all normal.

The patient died 6 months after presentation as a result of her metastatic breast cancer. Following steroid treatment, she had not experienced recurrence of her neurological symptoms.

DISCUSSION OF DIAGNOSIS

This presentation of neurological deficits in the setting of recurrent breast cancer is consistent with a paraneoplastic process, a rare complication in patients with breast cancer. The most commonly reported paraneoplastic neurological syndromes associated with breast cancer are paraneoplastic cerebellar degeneration, sensory and motor neuropathy, limbic encephalitis, opsoclonus–myoclonus, stiff-person syndrome, retinopathy, and Lambert–Eaton syndrome. A review published in 2003 found only 31 patients with breast cancer and associated paraneoplastic neurological syndromes reported in the literature.¹ Among paraneoplastic myelopathies, also referred to as necrotizing myelopathies,² lung cancer is the most commonly reported associated malignancy, followed by breast cancer. Supplementary Table 1 gives an overview of cases of paraneoplastic myelopathy and associated malignancy reported in the English-language literature over the last 20 years.

This is the first reported case of a possible paraneoplastic syndrome associated with the NMO (or aquaporin 4 [AQP4]) antibody. Lennon *et al.* first described this antibody in 2004 as a biomarker to differentiate between NMO and multiple sclerosis (MS).³ NMO, also known as Devic's disease, is a severe demyelinating disease originally described as affecting the optic nerves and spinal cord. The majority of cases follow a relapsing–remitting rather than a monophasic disease course. The NMO antibody binds to AQP4,⁴ the most abundantly expressed water channel in the brain. AQP4 provides a principal molecular pathway for brain permeability to water and has a key role in the development of brain edema.⁵ Since the identification of the NMO antibody, and following recent reports that some patients with NMO have non-specific subcortical white matter changes,⁶ the original

Table 1 Summary of laboratory evaluation in a patient with myelopathy in the setting of metastatic breast cancer.

Variable	Results	Reference range
Metabolic and autoimmune evaluation		
Comprehensive metabolic panel including liver function test	Normal	Normal
Troponin	80 µg/l	<50 µg/l
Vitamin B ₁₂	1,396.30 pmol/l	>154.98 pmol/l
IgA	1.33 g/l	0.89–5.81 g/l
Transglutaminase antibody	<15 units	<20 units
Rheumatoid factor	41 IU/ml	<40 IU/ml
Antinuclear antibody	<40	<40
Erythrocyte sedimentation rate	29 mm/h	0–15 mm/h
Tumor marker analysis		
CA 19-9	Elevated at 65 U/ml	<36 U/ml
CA 27-29	Elevated at 50 U/ml	<38 U/ml
CA 15-3	52 U/ml	<31 U/ml
CEA	4 µg/l	<4.7 µg/l
CSF analysis		
White blood cell count	0.009 × 10 ⁹ /l	<0.006 × 10 ⁹ /l
Red blood cell count	0.002 × 10 ⁹ /l	None × 10 ⁹ /l
Protein	0.86 g/l	0.15–0.5 g/l
Glucose	40 mg/dl (2.222 mmol/l)	40–70 mg/dl (2.22–3.89 mmol/l)
IgG index	0.6	0.3–0.6
Oligoclonal bands	None	None
CSF microbiology	Negative for JCV, HSV, VZV PCRs and VDRL test; negative culture	Negative
Serum paraneoplastic evaluation		
ACE receptor antibody	Negative	Negative
Striatal muscle antibody	Negative	Negative
N-type calcium channel antibody	Negative	Negative
P/Q-type calcium channel antibody	Negative	Negative
PCA-Tr	Negative	Negative
CRMP-5 IgG	Negative	Negative
ANNA-1,2,3	Negative	Negative
PCA-1	Negative	Negative
Amphiphysin antibody	Negative	Negative
Ganglionic acetylcholine receptor antibody	Negative	Negative
CSF paraneoplastic evaluation		
ANNA-1,2,3	Negative	Negative
CRMP-5 IgG	Negative	Negative
Amphiphysin antibody	Negative	Negative
PCA-1,2	Negative	Negative
PCA-Tr	Negative	Negative
Demyelinating conditions evaluation		
NMO antibody	Positive	Negative
IgG index	0.6	0.3–0.6
Oligoclonal bands	None	None

Abbreviations: ACE, angiotensin-converting enzyme; ANNA, anti-neuronal nuclear antibody; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CRMP-5, collapsing response mediator protein 5; CSF, cerebrospinal fluid; HSV, herpes simplex virus; IU, international units; JCV, JC virus; NMO, neuromyelitis optica; PCA, Purkinje cell cytoplasmic antibody; VDRL, venereal disease research laboratory; VZV, varicella-zoster virus.

proposed diagnostic criteria for NMO have been modified to reflect the new concept of NMO-spectrum disorders, including NMO, isolated optic neuritis, the Japanese form of optic-spinal MS, and recurrent longitudinally extensive transverse myelitis.⁷ This case represents a novel presentation of NMO-associated disease. To date, it is not understood what triggers the production of NMO antibodies or whether the antibodies directly cause the observed inflammatory response. It is conceivable that, in this case, the patient's metastatic breast cancer altered her immune status, making her more susceptible to inflammation, and that she developed a limited form of NMO presenting as longitudinally extensive transverse myelitis. We speculate, however, that NMO antibody production was triggered by an immune response against the patient's breast cancer, causing a paraneoplastic syndrome.

DIFFERENTIAL DIAGNOSIS

The patient in this Case Study presented with rapidly progressing myelopathic symptoms. The differential diagnosis of such symptoms includes conditions associated with breast cancer such as spinal cord compression from metastasis, metastasis within the spinal cord, a paraneoplastic syndrome, or a late effect of radiation therapy. Potential infectious etiologies include varicella-zoster virus or herpes simplex virus; the possibility of a causative infectious agent is particularly relevant considering this patient's history of immunosuppression. Metabolic causes could include vitamin B₁₂ deficiency. Immune-mediated etiologies of myelopathy—such as celiac disease, with which this patient was presumptively diagnosed previously—have been reported to present with an NMO-like picture.⁸ Demyelinating conditions such as MS or NMO-spectrum disorder should also be considered.

Gross spinal metastases within or around the spinal cord were excluded in this patient by PET scan and spinal MRI. Tests were negative for the infectious, celiac-related and metabolic neurological diseases outlined above. A demyelinating disease such as MS was not likely given the patient's overall clinical presentation, the appearance of the spinal cord lesion,⁹ the lack of demyelinating brain lesions, and the absence of oligoclonal bands in the patient's cerebrospinal fluid. Another possibility is that the patient presented with a NMO-spectrum disorder in the form of a recurrent transverse myelitis,



Figure 1 Spinal MRI results before and after treatment with corticosteroids. (A) T2-weighted sagittal thoracic spine images taken at the time of presentation show fusiform central cord signal abnormality, and cord expansion from C5 through T10. (B) T2-weighted sagittal images of the thoracic spine from 1 month after treatment with steroids show marked improvement of the previous cord signal abnormality. Compared with its appearance in (A), the spinal cord does not seem expanded and demonstrates minimal signal abnormality.

and the expression of the NMO disorder was influenced by her underlying breast cancer. We suspected a paraneoplastic syndrome because the patient had experienced similar symptoms more than 1 year previously, concurrent with progression of metastatic breast cancer. During the current episode, the patient was similarly found to have additional metastases, and also tested positive for the NMO antibody, which had not been tested for during the previous episode. Subsequent evaluation for NMO-like disease was performed; neuro-ophthalmological examination was normal, as were results of tests of brainstem auditory-evoked and visual-evoked potentials. These results do not exclude a limited form of NMO presenting as recurrent longitudinally extensive transverse myelitis; however, the close temporal relationship of acute myelopathy with recurrence of breast cancer on two separate occasions indicates that, in this case,

Acknowledgments

The authors thank Dr Vanda A Lennon for performing the testing for the neuromyelitis optica antibody.

Competing Interests

The authors declared no competing interests.

the NMO antibody was part of a paraneoplastic syndrome. A longer follow-up would have been necessary in order to definitely determine if the final diagnosis was a paraneoplastic syndrome or a NMO-spectrum disorder.

TREATMENT AND MANAGEMENT

Paraneoplastic diseases are primarily managed by treating the underlying cancer and by immunomodulatory therapy, although no established protocols are available. In this case, the patient was started on capecitabine therapy because the metastatic cancer had progressed on the prior chemotherapy regimen. In addition, the patient was treated for the brain metastases with gamma knife surgery. Finally, we treated the patient's myelopathy by the use of intravenous steroids, with outstanding results. In patients with NMO, the first-line therapy is intravenous corticosteroids, classically methylprednisolone sodium succinate 1 g/day for 5 days, followed by an oral steroid taper regimen—a strategy that we followed in this patient.¹⁰ These recommendations are based on case series and expert opinion rather than data from clinical trials. Second-line treatment, which was not required in this patient, includes plasmapheresis or intravenous immunoglobulin.¹¹ Currently, there is no consensus on the optimum therapy to prevent recurrence in patients with relapsing transverse myelitis;¹² options include immunosuppressive agents such as azathioprine, rituximab,¹³ or mycophenolate mofetil.

CONCLUSIONS

This Case Study demonstrates the first reported instance of myelopathy associated with the NMO antibody in the setting of metastatic breast cancer, and might represent an NMO antibody associated paraneoplastic syndrome. The diagnosis of paraneoplastic myelopathy is supported by the timely correlation of the myelopathy with recurrence of the breast cancer on two separate occasions; on the second occasion the myelopathy was also associated with the abnormal presence of an antibody that is strongly linked to myelopathic disease. An intriguing model for the underlying pathogenesis depicts an unknown antigenic stimulus leading to the production of NMO antibodies. These antibodies then bind

AQP4, activate the complement system and, ultimately, initiate a robust inflammatory response.¹² In this case, a potential initiating factor might be an antigen response to tumor cells. The cascades of molecular events leading to NMO antibody production and subsequent pathogenesis of NMO remain unknown, but will prove critical to the development of novel treatment strategies. This case broadens the differential diagnosis of paraneoplastic myelopathy and expands the spectrum of diseases associated with the NMO antibody. Further work is needed to help understand the role of the NMO antibody in malignancies and in paraneoplastic disease.

Supplementary Information in the form of a table is available on the *Nature Clinical Practice Neurology* website.

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