Published in final edited form as:
J Neurooncol. 2008 November ; 90(2): 213–216. doi:10.1007/s11060-008-9650-1.

Paraneoplastic opsoclonus-myoclonus ataxia associated with non-small-cell lung carcinoma

Kiran Musunuru[1] and **Santosh Kesari**[2,3,4]

1 *Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston,MA 02115, USA*

2 *Center For Neuro-Oncology, Dana-Farber Cancer Institute, SW 460, 44 Binney Street,Boston, MA 02115, USA*

3 *Department of Neurology, Division of Cancer Neurology, Brigham and Women's Hospital,75 Francis Street, Boston, MA 02115, USA*

4 *Harvard Medical School, Boston, MA, USA*

Abstract

We report a case of the paraneoplastic opsoclonus-myoclonus ataxia syndrome in a patient with non-small cell lung carcinoma, which represents a highly unusual association. The patient simultaneously manifested both severe neurologic symptoms and widely metastatic disease, complicating her treatment.

Keywords

Paraneoplastic opsoclonus-myoclonus ataxia; Non-small cell lung cancer; Anti-Ri antibody

Introduction

Paraneoplastic neurologic disorders (PNDs) are rare syndromes that arise as a result of an anti-tumor/anti-neuronal immune response in the setting of a tumor expressing proteins ("onconeural" antigens) normally restricted in expression to the nervous system (1). A variety of PNDs and their associated onconeural antigens have been identified, with the antigens found to play critical roles in neuronal function (2). Paraneoplastic opsoclonus-myoclonus-ataxia (POMA), a clinical syndrome whose symptomatology is described by the name, is most sometimes associated with high-titer autoantibodies in blood and/or cerebrospinal fluid (CSF) that recognize two closely related neuronal RNA-binding proteins designated Nova-1 and Nova-2 (3,4). These antibodies are variously known in the literature as "anti-Ri" and "ANNA-2" (type 2 anti-neuronal nuclear autoantibody) (5,6).

Anti-Ri antibodies are most commonly seen with breast cancer but have been reported in association with ovarian, fallopian, lung, bladder, and gastric tumors (5,6). While there is a strong correlative (and presumably causative) relationship between anti-Ri antibodies and POMA, the antibodies have been observed in other PNDs, including paraneoplastic brainstem encephalitis (7) and stiff-person syndrome (8). Many patients have occult tumors that are recognized only after patients have presented to clinical attention for their neurologic symptoms, and in some patients a tumor is never found. Because PNDs are thought to directly result from either antibody-mediated and/or cytotoxic-T-cell-mediated mechanisms (9,10),

Corresponding author: Santosh Kesari, skesari@partners.org.

empiric immunosuppressive therapy is often administered in an attempt to treat the symptoms; durable responses have been reported, but only on an anecdotal basis. It is generally considered that removal of the underlying tumor, if one can be found, is the first-line therapy for the neurologic disease.

We report a case of a patient with metastatic non-small-cell lung carcinoma who exhibited the hallmark features of the POMA syndrome and was found to harbor high-titer anti-Ri antibodies. Despite attempts at immunosuppressive therapy, the patient's performance status did not improve to the point that aggressive therapy of her metastatic disease could be undertaken, illustrating the unique challenges inherent in the treatment of PNDs.

Case report

The patient is a 63-year-old female who was otherwise healthy when she developed dizziness, vertigo, nausea, headaches, and gait instability. She was initially thought to have a labyrinthitis and was unsuccessfully treated with meclizine. During the month following the emergence of her symptoms, she experienced fatigue and weight loss, prompting admission to an outside hospital during which she was found to harbor a right lung upper lobe mass on chest radiography; follow-up computed tomography imaging confirmed the presence of a lobulated necrotic mass with enlarged subcarinal and paratracheal lymph nodes, biopsy of which diagnosed non-small-cell lung carcinoma.

Per outside hospital, she was noted on physical examination to have enhanced lateral beating "nystagmus" with lateral gaze bilaterally, intermittent left beating "nystagmus" with upgaze, intermittent opsoclonus, mild lingual dysarthria, mild arm dysmetria with coarse intention tremor bilaterally, and severe truncal ataxia preventing her from sitting upright in bed. Magnetic resonance imaging (MRI) showed non-specific scattered foci of abnormal T2 prolongation in the subcortical and periventricular white matter and inflammatory T2 lesions in the right midbrain and cerebral peduncle without enhancement (Fig. 1a, b). Cerebrospinal fluid obtained by lumbar puncture showed lymphocytic pleocytosis (RBC 40; WBC 90–95% lymphocytes, 3% monocytes, 2% macrophages; protein 75, glucose 62) with negative cultures and negative cytology for malignant cells on two separate lumbar punctures. She soon thereafter underwent right thoracotomy with upper lobectomy and radical lymph node dissection. Pathologic analysis of the specimens revealed poorly differentiated carcinoma in the original tumor as well as in the lymph nodes, although the cells from the lymph node metastases exhibited different marker profiles, suggesting differentiation from the original tumor.

After a month of symptoms she was transferred to our hospital and because of high suspicion of a PND, despite two negative screens for paraneoplastic antibodies by a commercial service, she received a short course of intravenous steroids (1 g IV/day × 3 days) and oral steroid taper over 4 weeks (intravenous immunoglobulin (IVIG) was not available at the time due to a national shortage), upon which her ataxia and opsoclonus improved but still debilitating. Because of her poor functional status from debilitating neurological symptoms and weight loss over this time, the primary oncology service deferred treatment until neurological improvement. Unable to participate in physical therapy due to continued vertigo and gait instability, she was readmitted after several weeks to the neurology service. At that time, she was noted to still have severe opsoclonus, ataxia, and mild myoclonus and dysmetria in upper extremities without other cerebral or brainstem symptoms. Repeat MRI showed improvement in the T2 changes in the brainstem noted previously (Fig. 1c, d) consistent with response to steroid treatment or natural evolution of paraneoplastic disease.

Because of continued suspicion of a PND despite negative commercial paraneoplastic antibody screening by western blot and ELISA (Athena Diagnostics, Worcester, MA, USA; http://www.athenadiagnostics.com), and especially POMA because of the symptoms, the patient's serum was more carefully screened in our own laboratory for the presence of paraneoplastic antibodies (Fig. 2). The patient's serum was found to harbor high-titer (>1:500) anti-Ri antibodies, consistent with a clinical diagnosis of POMA. At this time the patient was discovered to harbor lesions in the liver by computed tomography imaging. Presumptively diagnosed as metastatic lesions, they were sampled by imaging-guided biopsy to rule out a second tumor that had more neuroendocrine features typically associated with POMA and found to harbor cells similar to those seen in the lymph node metastases.

Repeat imaging of the brain showed several small punctate focus of enhancement in the cerebellar and cerebral hemispheres concerning for metastatic parechymal disease without leptomeningeal enhancement. Spinal imaging also did not reveal leptomeningeal or spinal metastases and repeat CSF studies were negative for malignancy. Subsequent whole body F18-FDG positron emission tomography (PET) documented metastasis to more mediastinal and hilar lymph nodes—the brain lesions were too small to be detected by PET. The patient received a second course of high-dose steroids (1 g IV/day × 3 days) with IVIG (now available; 0.4 g/kg/day × 5 days) as well as two weeks of whole-brain radiation therapy. Her symptoms improved markedly and she was more alert, communicative, and able to keep her eyes open for extended periods of time. She nevertheless was unable to participate in physical therapy due to severe opsoclonus and ataxia. Many different drugs were tried to control the opsoclonus in hopes of being able to start chemotherapy but these had minimal effect. Over the next couple of months her condition deteriorated again as the metastatic disease spread further. Due to her poor performance status the thoracic oncology team did not offer standard chemotherapy. Although she did eventually start erlotinib (epidermal growth factor receptor inhibitor) therapy for a brief time, she ultimately opted for hospice care due to her severe neurological symptoms and passed away shortly thereafter. Autopsy was declined.

Results

Anti-Ri antibodies

We screened the patient's serum against a lysate of whole mouse brain by Western blot analysis, which identified a set of bands that confirmed that the serum contained antibodies against a protein or proteins expressed in brain (data not shown). We then tested the patient's serum, along with well-characterized sera from other patients known to be reactive against the Ri, Hu, and Yo onconeural antigens, against either recombinant Nova-1 protein or mouse cerebellum in Western blot analysis (Fig. 2). The patient's serum contained antibodies that recognized both recombinant protein and cerebellar antigens in identical fashion as anti-Ri serum, establishing that the patient harbored high-titer anti-Ri antibodies.

Pathologic specimens

Samples of the primary tumor, obtained from lobectomy, was characterized as poorly differentiated adenocarcinoma of an acinar type. Immunohistochemistry performed on paraffin sections showed positivity in the tumor cells for TTF-1, CK7, and beta-catenin, and negativity for CK20 supporting the diagnosis of primary lung adenocarcinoma. Two lymph nodes removed during the same surgical procedure were found to have metastatic poorly differentiated carcinoma. The cells in the lymph nodes exhibited different marker profiles, suggesting differentiation from the original tumor—positivity for TTF-1, CK7, AE1/AE3, and chromogranin, and negativity for CK20, synaptophysin, S-100, and hepar1. The cells obtained from the subsequent fine needle aspiration of a liver lesion were notable in that they were also similar to the lymph nodes metastatic cells with the same differentiation marker profiles

suggesting origin from primary lung tumor. Despite extensive review, none of these specimens showed features of neuroendocrine differentiation suggestive of a small-cell component that is typically associated with POMA.

Immunohistochemistry was performed using patient's serum on paraffin embedded sections of all 3 tumor samples and with multiple repeats. These samples did not show any positive cells, suggesting either a sampling problem or that the immune response was controlling the growth of a subset of tumor cells expressing Nova antigens that were not detected in our limited biopsy sampling of tumors. Unfortunately, patient's family declined autopsy and we are unable to confirm this hypothesis.

Discussion

We were able to establish a diagnosis of the rare POMA syndrome in this patient with non-small-cell lung carcinoma. POMA is most commonly associated with breast and ovarian cancer, and when coincident with lung cancer it is typically associated with small-cell lung carcinoma. We were only able to find a very limited number with non-small-cell lung carcinoma reported in the literature (6,11). As with those cases, we cannot definitively prove a causal relationship between the primary tumor and the neurologic disease. Nevertheless, the time course is extremely suggestive, with the patient's first neurologic symptoms emerging at essentially the same time as the diagnosis of the primary lung tumor, which by then had already metastasized to lymph nodes.

PNDs are believed to arise from an immune response to tumor-expressed proteins that are not recognized as "self" because they are restricted in expression to the central nervous system, which is shielded from immune surveillance by the blood–brain barrier (1). In order for our patient to have developed POMA, then, it seems likely that some cells within the primary lung tumor expressed Nova proteins, the antigens recognized by anti-Ri antibodies. Although it would be unusual for a non-small-cell lung carcinoma to express neuron-specific proteins, as these tumors do not typically have neuroendocrine features, the degree of undifferentiation observed with these cells by pathologic analysis may have favored the production of some number of neuronal proteins including Nova. We investigated immunostaining of our patient's tissues but were unable to confirm this hypothesis which may be due to sampling error or to the immune response to this subset of cells.

This case highlights the difficulties associated with the treatment of PNDs, in which the patient suffers from both the underlying oncologic condition as well as the neurologic symptomatology. Many patients succumb to the neurologic disease rather than the cancer. Although our patient's neurologic symptoms modestly improved with immunosuppressive treatment, the patient's performance status did not improve sufficiently to allow for aggressive treatment of the metastatic disease with chemotherapy. Unfortunately, there was an over 1-month delay in diagnosis from original presentation at outside hospital which may have contributed to the irreversibility of her neurological symptoms. Also, because of negative commercial screening for PNDs, treatment was delayed which might have halted the neurological symptoms. Thus, our inability to fully address one of the patient's conditions prevented optimal treatment of the second condition, which in turn further impaired the treatment of the first condition. Earlier diagnosis and initiation of treatment for her paraneoplastic disorder might have prevented this downward cycle. Having a centralized national PND research laboratory to corroborate such cases may have facilitated earlier diagnosis. The patient eventually succumbed to a combination of the sequelae of neurologic dysfunction as well as malignancy.

Acknowledgements

The authors would like to thank Dr. Robert Darnell and members of his laboratory for their advice and assistance with screening for paraneoplastic antibodies.

References

1. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543–1554. [PubMed: 14561798]
2. Musunuru K, Darnell RB. Paraneoplastic neurologic disease antigens: RNA-binding proteins and signaling proteins in neuronal degeneration. Annu Rev Neurosci 2001;24:239–262. [PubMed: 11283311]
3. Buckanovich RJ, Posner JB, Darnell RB. Nova, the paraneoplastic Ri antigen, is homologous to an RNA-binding protein and is specifically expressed in the developing motor system. Neuron 1993;11:657–672. [PubMed: 8398153]
4. Yang YY, Yin GL, Darnell RB. The neuronal RNA-binding protein Nova-2 is implicated as the autoantigen targeted in POMA patients with dementia. Proc Natl Acad Sci USA 1998;95(22):13254–13259. [PubMed: 9789075]
5. Luque FA, Furneaux HM, Ferziger R, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. Ann Neurol 1991;29:241–251. [PubMed: 2042940]
6. Pittock SJ, Lucchinetti CF, Lennon VA. Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol 2003;53:580–587. [PubMed: 12730991]
7. Rajabally YA, Naz S, Farrell D, Abbott RJ. Paraneoplastic brainstem encephalitis with tetraparesis in a patient with anti-Ri antibodies. J Neurol 2004;251:1528–1529. [PubMed: 15645357]
8. McCabe DJ, Turner NC, Chao D. Paraneoplastic “stiff person syndrome” with metastatic adenocarcinoma and anti-Ri antibodies. Neurology 2004;62:1402–1404. [PubMed: 15111682]
9. Levin MC, Lee SM, Kalume F, et al. Autoimmunity due to molecular mimicry as a cause of neurological disease. Nat Med 2002;8:509–513. [PubMed: 11984596]
10. Albert ML, Darnell JC, Bender A, et al. Tumor-specific killer cells in paraneoplastic cerebellar degeneration. Nat Med 1998;4:1321–1324. [PubMed: 9809559]
11. Erlich R, Morrison C, Kim B, et al. ANNA-2: an antibody associated with paraneoplastic opsoclonus in a patient with large-cell carcinoma of the lung with neuroendocrine features—correlation of clinical improvement with tumor response. Cancer Invest 2004;22:257–261. [PubMed: 15199608]

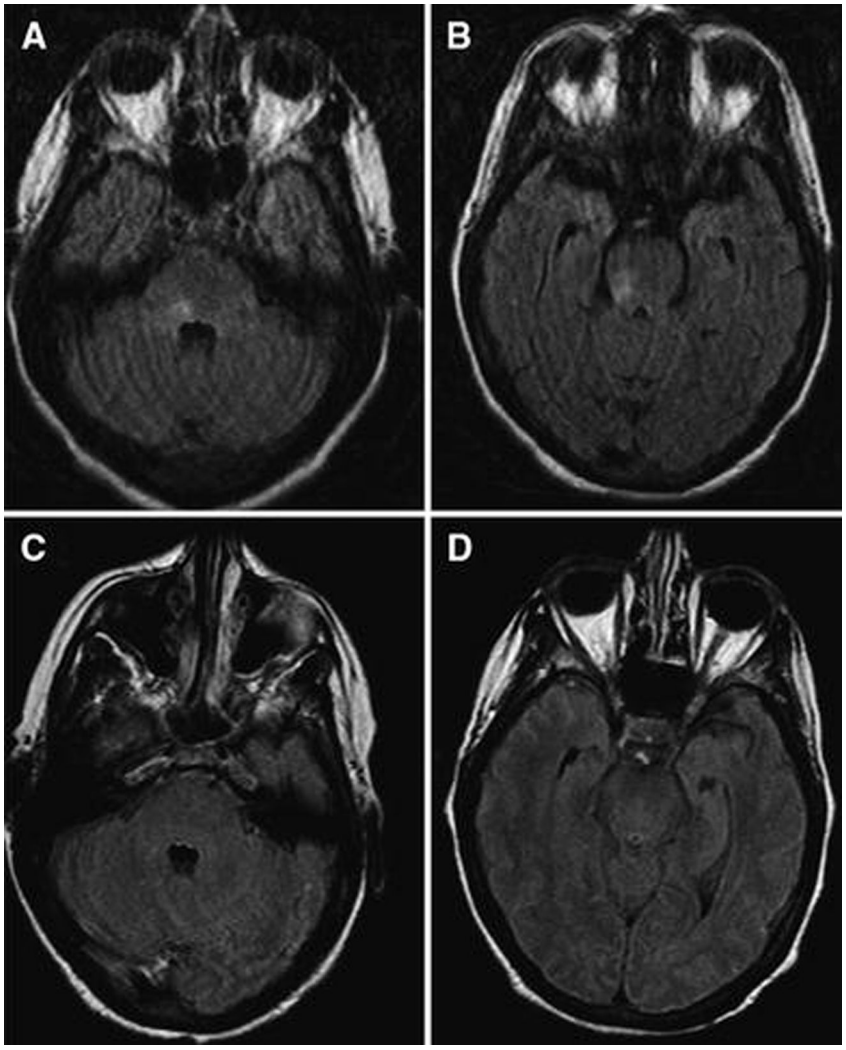

Figure 1.
FLAIR-weighted MRI images. Serial axial FLAIR images from presentation (a, b) and 1 month after treatment with steroids (c, d) demonstrate resolution of FLAIR lesions in brainstem

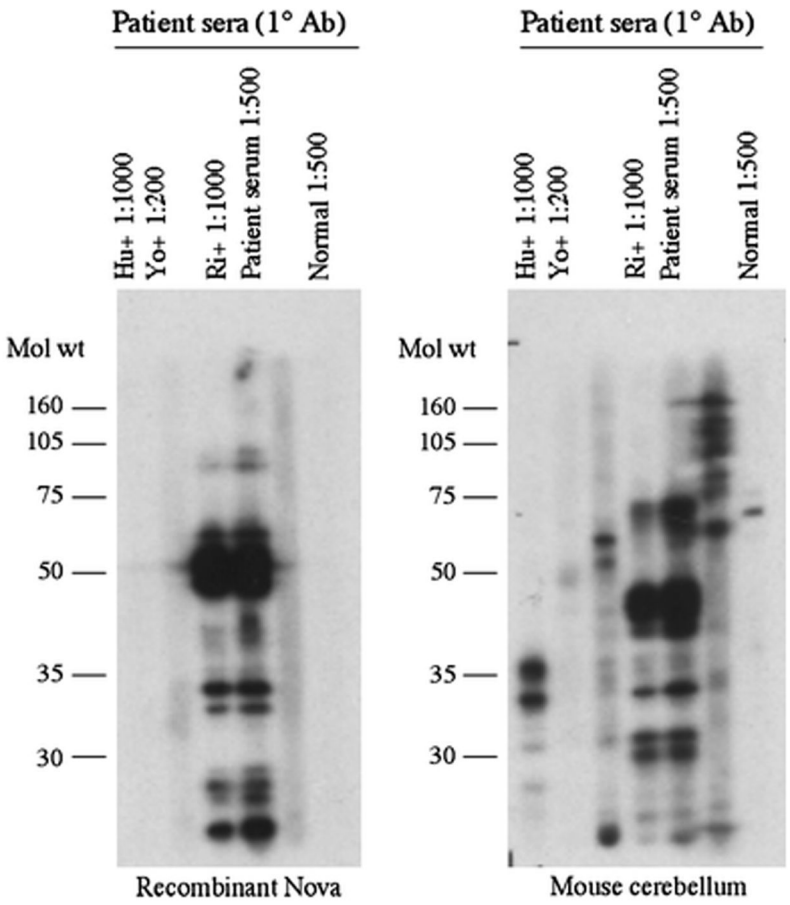

Figure 2.

Western blot analysis using patient serum as primary antibody. We tested the patient's serum, along with well-characterized sera from other patients known to be reactive against the Ri, Hu, and Yo onconeural antigens, against either recombinant Nova-1 protein (left panel) or mouse cerebellum (right panel) in Western blot analysis. The patient's serum contained antibodies that recognized both recombinant protein and cerebellar antigens in identical fashion as anti-Ri serum, establishing that the patient harbored high-titer anti-Ri antibodies