Acute Myeloid Leukemia Presenting as Autoimmune Autonomic Ganglionopathy

Joel N. Phillips, DO; Elmotaz Ibrahim, MD; Javier A. Arias-Stella III, MD; Mirela Cerghet, MD; Naganand Sripathi, MD*

Abstract—Autoimmune autonomic ganglionopathy (AAG) is a paraneoplastic syndrome characterized by antibodies against neuronal Ach ganglionic (alpha-3) receptors in the autonomic nervous system. It is rarely associated with malignancy. A 59 year old male reported orthostatic hypotension for two years. Preliminary neurologic and cardiac evaluations were unremarkable. Paraneoplastic studies revealed neuronal AChR Ganglionic (alpha-3) antibodies. His chest CT demonstrated an enlarged subcarinal lymph node. A PET scan and IVIG were offered, but initially refused. Pancytopenia, bruising, weight loss, and fatigue ensued. A bone marrow biopsy revealed acute myeloid leukemia (AML). This is the first known case of AAG associated with AML.

Keywords —acute myeloid leukemia, autoimmune autonomic ganglionopathy, myelodysplastic disorder, paraneoplastic syndrome.

I. INTRODUCTION

Autoimmune autonomic ganglionopathy (AAG) refers to an autonomic neuropathy, most often an idiopathic monophasic illness with slow progression and incomplete recovery. Antibodies against neuronal Ach ganglionic (alpha-3) receptors were recently identified and may be detected in about 50% of patients with idiopathic or paraneoplastic autonomic neuropathies. AAG can affect the sympathetic, parasympathetic, and enteric nervous systems. Patients with AAG typically present with severe autonomic failure including orthostatic hypotension, anhidrosis, pupillary abnormalities, gastrointestinal dysmotility, and bladder disturbances. One reported patient with AAG experienced severe bradycardia necessitating a pacemaker. Autonomic studies were consistent with a denervated heart. Another reported patient complained of severe gastric dysmotility with postprandial vomiting after any liquid or solid food intake.

The patient had been experiencing hypotensive episodes for two years. A tilt table test at that time revealed blood pressures of 125/74, 103/64, and 87/55 mmHg, and pulse of 74, 77, and 78 bpm recorded from lying, sitting and standing respectively. With addition of isoproterenol, his blood pressure was 118/71 and a pulse of 87. Antihypertensive medications were stopped by his primary care doctor as his episodes become more frequent and severe. On admission, he mentioned 7 to 8 additional falls, including multiple fractures, prior to his episodes. One reported patient with AAG had presented with a denervated heart.

He was found to be normotensive. Orthostatic vital signs were positive. His systolic blood pressure changed from 123 to 89 mmHg upon standing to sitting, with a pulse change from 103 to 89 bpm. An MRI of the brain was performed, showing chronic ischemic changes, but otherwise negative for intracranial pathology. He was evaluated by cardiology. A stress echo failed to reveal a cardiac abnormality. A holter monitor had revealed sinus bradycardia to the 40’s and sinus tachycardia to 120’s. AM cortisol had been measured and found to be low; a repeat test was normal. Catecholamines had also been tested, found to be normal. Imaging was negative for adrenal masses. A CT scan of the chest revealed an enlarged subcarinal lymph node at 1.1 cm.
He was transferred to the inpatient neurology service; an EMG for autonomic insufficiency was partially performed, with completion at a later date as an outpatient. RR variability was 12, and an E/I ratio was 1.15. This was within range of age related normal. He underwent a lumbar puncture with unimpressive results. Oligoclonal bands were negative as well as IgG index. His CSF was not sent for cytology. He was treated with intravenous hydration and fludrocortisone. He was discharged with improvement in his orthostatic vital signs, and a paraneoplastic panel was pending.

The patient followed up in the clinic one month later with progressive symptoms. In the interim, he began to use a walker to ambulate, as he again was feeling lightheaded with postural changes. His results of the paraneoplastic panel were reviewed. He was found to have neuronal Ach Ganglionic (alpha-3) receptor antibodies at 0.29 nmol/L, within the intermediate range. This was consistent with AAG. A PET scan was ordered, but was never completed.

He again followed up in two months. Systolic blood pressure was 59 mmHg on presentation to the clinic with a repeated measurement at 74 mmHg. His fludrocortisone was increased. The patient was then lost to follow up, with repeated attempts to contact him and initiate therapy with intravenous immunoglobulin therapy (IVIG) or plasmapheresis.

Two months later, his wife reported increased fatigue and confusion. His systolic blood pressure was measured at home and found to be 50 mmHg. He delayed seeking emergent treatment for several days. Eventually, he demonstrated interest in starting therapy with IVIG. He reported frequent falls, increased bruising, and a 40 pound weight loss over the last month.

On presentation, orthostatic vital signs were again found to be positive: lying blood pressure was 110/60 mmHg, and standing blood pressure was 62/48 mmHg. He was admitted to the general medicine floor. He received his first treatment of IVIG, when a repeat CT scan of the chest showed enlargement of his mediastinal lymph node to 1.3 cm. A routine blood test revealed pancytopenia. His Coomb’s test was negative and his LDH, haptoglobin, and reticulocyte count were within normal limits. A peripheral blood smear was suggestive of a myelodysplastic disorder.

The patient then underwent a bone marrow biopsy, which was diagnostic for acute myeloid leukemia, based on background dysplasia, blast morphology (Figure 1 and 2 respectively), and immunohistochemical staining with myeloperoxidase, CD34, CD117, CD68. These findings were consistent with AML.

Chemotherapy was considered, after the diagnosis was made. However, given his comorbidities, including renal failure and the development of aspiration pneumonia, he was admitted to hospice, and died 24 hours later.

Fig. 1. H&E stain of bone marrow demonstrating hypercellularity to 80-90%, with infiltration of immature monocytes (100x).

Fig. 2. Peripheral smear representing a typical myeloblast (1000x)

III. DISCUSSION

This case represents the first description of AAG as a manifestation of a paraneoplastic syndrome prior to diagnosis of AML.

AAG is considered an antibody-mediated neurological disorder caused by impairment of synaptic transmission in sympathetic, parasympathetic and enteric autonomic ganglia generally due to an idiopathic process. Ganglionic AchR antibodies bind to ganglionic (alpha3-type) neuronal AchR, a ligand-gated cationic channel receptor.

Paraneoplastic syndromes are rare dysfunctions of the nervous system in patients with malignancies. Often, paraneoplastic syndromes present prior to manifestation of tumors, or detectable malignancy. In patients with antibodies targeting intracellular onconeural antigens, almost all the time there is association with an underlying tumor. This is not the case with antibody targeting surface antigens: ion channels and receptor proteins. AAG is rarely found in patients with malignancies, but can be associated with SCC, and thymoma. There are also reports of association with rectal and thyroid malignancies.
Further screening in our case did warrant a PET scan. In retrospect, if performed for this patient, it was unlikely to produce positive results. When a classic paraneoplastic syndrome is discovered, diagnostics should be targeted toward the suspected malignancy associated with the specific syndrome or antibodies detected.9

Typical manifestations of patients who are seropositive for ganglionic AchR antibodies involve gastrointestinal dysmotility, anhidrosis, urinary hesitancy, bradycardia, orthostatic hypotension and occasional syncope.1 Multiple autonomic symptoms can be found in a single patient. Sympathetic and parasympathetic dysfunction is often seen on autonomic testing such as QSART and thermoregulatory sweat tests.1 Symptoms usually evolve over three to six weeks, and with treatment may resolve within three months to a year.1

As paraneoplastic syndromes are immune-mediated conditions, immune modulation is essential in the management of patients. This is in addition to the treatment of the underlying malignancy. Specific treatment modalities include corticosteroids, steroid sparing agents, Intravenous immunoglobulin and plasma exchange.11 In paraneoplastic syndromes where antibodies are detected, specific B-cell therapy, such as rituximab usually is considered. More aggressive treatment regimens that included combination of methyl prednisolone, cyclophosphamide and IVIG were employed in anti-Hu and anti-Yo syndromes with some success, but experience in AAG is limited.12

The patient in this case received one dose of IVIG. Although there is no standard dose of IVIG, many patients receive 0.4mg/kg per day for 3-5 days.9 This may need to be repeated on a monthly basis.9 Patients with AAG may respond to immunomodulatory therapy such as prednisone 1 gm given intravenously daily for 3-5 days, or plasmapheresis every other day for 5-6 doses repeated monthly or as necessary.2,9 Rituxumab may also be considered a first line therapy.9 In diseases with an antibody to surface antigens, the pathogenic role was attributed to B-cells with evidence of complement-mediated pathogenesis, demonstrated in patients with VGKC complex antibodies.10 This observation may explain the response to long term rituximab treatment of a patient with AGG.6 Furthermore, in central nervous system paraneoplastic disorders, rituximab depletes intrathecal B-cells, with an effect lasting up to 8 weeks.9 Dosing is typically 375 mg/m2 weekly for 4 weeks.9

Paraneoplastic phenomena have been associated with aggressive transformation of myelodysplastic syndrome.13 We found in literature one case report of a patient with known AML who developed progressive voltage gated potassium channel antibody mediated limbic encephalitis and had a fulminating course.14

Due to poor outcome of AML in older patients,15 for older patients with indolent AML, severe comorbidities, poor physical function or unfavorable risks, supportive care is suggested instead of aggressive therapy.

Despite the rarity of AAG reported as a paraneoplastic syndrome, screening for malignancy should be routinely performed, and specifically, diagnostic screening for AML can be considered.

IV. ACKNOWLEDGMENTS

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References


Questions (please choose a single answer):

1. Malignancies associated with AAG include:
   a. Small cell lung cancer
   b. Thymoma
   c. Glioblastoma
   d. A and B
   e. B and C

2. All of the following are symptoms of autonomic ganglionopathy except:
   a. Anhidrosis
   b. Urinary frequency
   c. Gastric dysmotility
   d. Orthostatic hypotension

3. Which of the following is true regarding AAG:
   a. It is a polyphasic disease with waxing and waning of symptoms
   b. Fully recovery is a rare event despite curative treatment
   c. Antibody titers correlate with the clinical severity of symptoms.
   d. Impairment is seen in synaptic transmission in sympathetic, parasympathetic and enteric autonomic ganglia

*Answers:* 1. D; 2. B; 3. D.