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# Paraneoplastic orthostatic hypotension associated with acute myeloid leukemia

S. LEE[1], M. CHARY[2], B. PETERSEN[3], J.O. MASCARENHAS[4]

[1]Department of Medicine, Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, Elmhurst, New York, USA
[2]Icahn School of Medicine at Mount Sinai, New York, New York, USA
[3]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[4]Tisch Cancer Institute, Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

**Abstract. – Paraneoplastic neuropathies associated with leukemia are rare, and early diagnosis and treatment are crucial due to the potential for irreversible neurological deficits and delay in treatment of the leukemia. This is the first report to describe severe paraneoplastic orthostatic hypotension which resolved after treatment of the acute myeloid leukemia (AML). The patient is a 76 year-old woman who presented with progressive dizziness, anorexia, and fatigue. She had severe orthostatic hypotension (supine systolic blood pressure 186 mmHg and standing 79 mmHg). She was found to have AML, for which azacitidine was initiated, and orthostatic hypotension resolved after initiation of treatment.**

**This case demonstrates a unique example of paraneoplastic sequelae remitting with treatment of the underlying hematologic neoplasm. Physicians should be aware of this unusual occurrence of autonomic neuropathy with AML as delay in treatment of the hematologic malignancy can lead to irreversible neurologic deficit and increased morbidity and mortality.**

*Key Words:*
Paraneoplastic syndrome, Acute myeloid leukemia, Orthostatic hypotension.

## Introduction

Paraneoplastic neuropathies (PNP) are pathologies of the nervous system associated with the paraneoplastic effects of a neoplastic disorder, as distinct from the neurological sequelae of metastases or chemotherapy[1]. These neuropathies encompass broad symptomatology, including sensorimotor neuropathy, autonomic dysfunction, vasculitic neuropathy, demyelinating neuropathy, and paraproteinemia[2]. The pathophysiology of PNP is not fully understood; autoimmune derangement, cell-mediated immunity, production of antibodies by the tumor, synthesis of hormone-like substances by the tumor, or competition between the neoplasm and the nervous system for resources have been suggested[1,3,4].

Solid malignancies, such as small cell lung cancer, ovarian, breast, and brain cancer are most frequently associated with PNP[5-7]. PNP is infrequently associated with leukemia, and when reported is confined to the peripheral nervous system[8].

Consensus guidelines for the treatment of PNP are lacking. Since those associated with leukemia are not mediated by autoimmune antibodies, therapeutic approach is focused on treatment of the underlying leukemia. However, most paraneoplastic neuropathies cause irreversible neurologic damage, and therefore, early diagnosis and treatment are crucial to lessen the morbidity associated with paraneoplastic disorders.

Here, we report a patient who presented with severe orthostatic hypotension and was subsequently found to have acute myeloid leukemia (AML) with trisomy 8. This unique case demonstrates paraneoplastic orthostatic hypotension that immediately resolved after initiation of AML therapy.

### Case Report

A 76 year-old woman with a past medical history of hypertension and hyperthyroidism status post radioiodine ablation 3 years ago and currently taking levothyroxine presented with progressive dizziness upon standing over the last two months. Additionally, she noted anorexia accompanied by a 10 pound weight loss and accompanying fatigue. The patient was found to have severe orthostatic hypotension (supine blood pressure 186/82 mmHg, heart rate 65/min; standing


*Corresponding Author:* John O. Mascarenhas, MD; e-mail: john.mascarenhas@mssm.edu

79/53 mmHg and 69/min). Her physical examination, including a full neurological examination, was otherwise unremarkable except for a violaceous maculopapular rash on the bilateral lower extremities. The patient's usual dose of metoprolol was held for orthostatic hypotension. Three liters of intravenous hydration did not lessen the orthostatic hypotension. Serial electrocardiograms showed no dysrhythmia. Cardiac enzymes were within normal range. A basic metabolic panel was unremarkable. A morning cortisol level and cosyntropin stimulation test were also unremarkable.

Complete blood count was remarkable for anemia (hemoglobin 7.9 g/dL, decreased from 11 g/dL three months prior), thrombocytopenia (platelets 21,000/μL, decreased from 240,000/μL three months prior), and white blood cell count of 13,300/μL with 44% blasts. Lactate dehydrogenase was elevated (502 U/L). Peripheral blood smears showed immature cells with vacuolated cytoplasm (Figure 1A). Flow cytometry of peripheral blood demonstrated an aberrant myeloid phenotype: CD33+, CD13 dim+, HLA-DR+, CD56+, CD4+, CD38+, CD11b dim+, CD15 dim+, CD7 partial dim+, CD34-, CD117-, CD14-, CD3-, CD5-, CD10-, and CD19-. Bone marrow aspiration and biopsy showed sheets of blasts comprising approximately 90% of overall cellularity (Figure 1B); immunoperoxidase stains performed on the biopsy revealed that neoplastic cells were also positive for CD43 and CD68, and negative for CD123; labeling for myeloperoxidase was equivocal. Trisomy 8 was detected by conventional karyotyping from the aspirate. BCR-ABL1, JAK2V617F, CCAAT/enhancer-binding protein alpha mutation, KIT mutation, FMS-like tyrosine kinase-3, and nucleophosmin-1 were not detected by polymerase chain reaction (PCR). A punch biopsy of the lower extremity rash was obtained and revealed lipodermatosclerosis with no evidence of neoplastic cells. Although the immunophenotype of the leukemic cells had some features of blastic plasmacytoid dendritic cell neoplasm (CD4+, CD56+, and CD34-), the diagnosis of acute myeloid leukemia was rendered on the basis of absence of immunohistochemical labeling for CD123 in conjunction with the identification of trisomy 8[9].

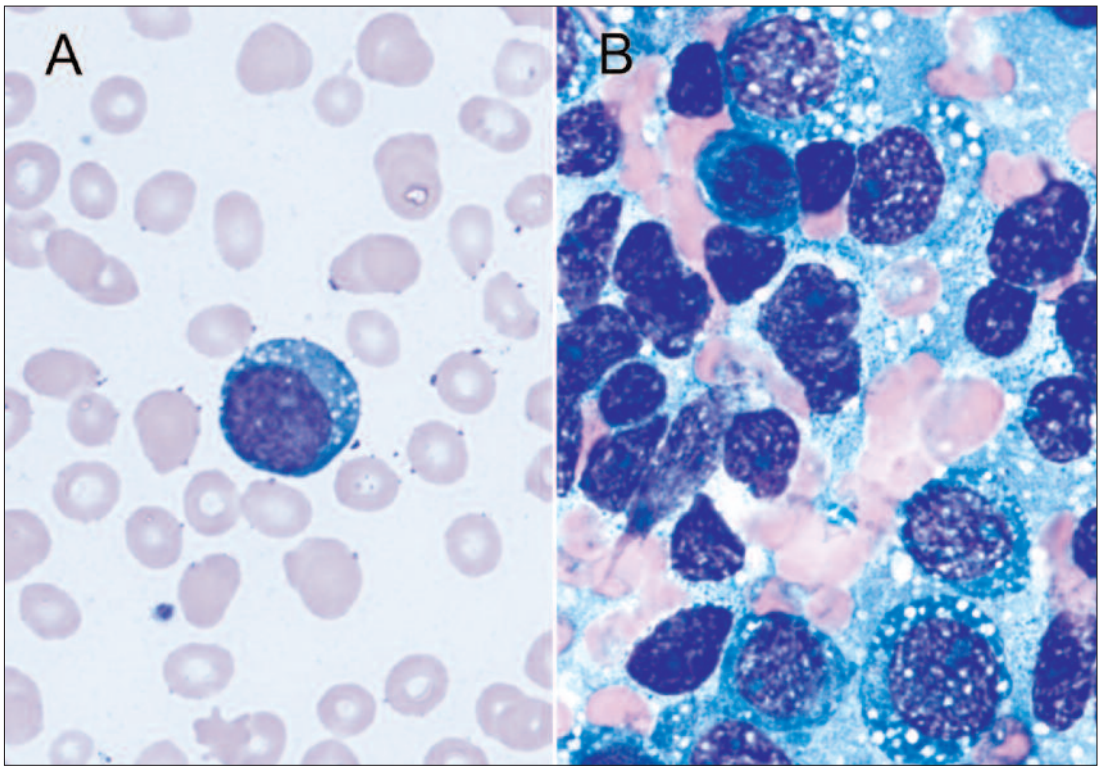


**Figure 1.** Peripheral blood and bone marrow aspirate smears. ***A,*** Peripheral blood smear showing a blast cell with a nucleolus and multiple cytoplasmic vacuoles (Wright Giemsa stain, ×1,000). ***B,*** Bone marrow aspirate smear with sheets of blasts similar to those in the peripheral blood (Wright Giemsa stain, ×1,000).

Treatment was initiated with subcutaneous azacitidine 75 mg/m$^2$ for 7 consecutive days. The patient tolerated this therapy well, and the orthostatic hypotension (supine blood pressure 118/68 mmHg, heart rate 67/min; standing 107/69 mmHg, 71/min) resolved 17 days after therapy was initiated. A repeat peripheral blood smear demonstrated resolution of peripheral blood blasts.

## Discussion

The diagnosis of a paraneoplastic neuropathy in leukemia is usually based on clinical signs and symptoms due to the lack of detectable autoimmune antibodies[8]. The resolution of symptoms during the course of azacitidine is sufficient to diagnose this autonomic instability as a PNP[10]. This patient's neurological disorder is categorized as a "definite" paraneoplastic neurological syndrome, based on the criterion established by Graus et al: "A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission"[10].

Classifications aside, the most likely cause of the patient's orthostatic hypotension was a paraneoplastic effect. A supra-therapeutic dose of metoprolol could explain fatigue and orthostatic hypotension. However, both symptoms began long after starting metoprolol, were not associated with any change in dosage, and did not abate when metoprolol was stopped. Dehydration was an unlikely cause because the patient had no electrolyte abnormalities or increase in blood urea nitrogen level, and the problem persisted after adequate IV hydration. Neither medication nor dehydration would likely cause a significant drop in systolic blood pressure by over 100 mmHg on standing. A complete neurological examination showed no evidence of cerebellar dysfunction, parkinsonism, or multi-system atrophy. Adrenal insufficiency is unlikely in the setting of a normal cortisol level and unremarkable cosyntropin stimulation test. Therefore, paraneoplastic orthostatic hypotension is the most likely cause of this patient's complaint although rare, and especially rare in patients newly diagnosed acute leukemia.

Under the umbrella of autonomic dysfunction, orthostatic hypotension may occur more widely but be underreported: it is not life-threatening compared to other paraneoplastic neurological syndromes associated with demyelination or inflammation, and therefore, not well recognized. In addition, autonomic dysfunction develops along with at least one other paraneoplastic neurologic syndrome in other cancer types[6].

There is no consensus for the treatment of PNP that fails to resolve with chemotherapy. Suggested treatment options include high dose intravenous immunoglobulin, corticosteroids, plasmapheresis, or immunosuppression[6,11]. When orthostatic hypotension is accompanied by other neurologic signs and symptoms that suggest inflammation or demyelination, these treatment options may prevent further neurological damage[12]. The patient's paraneoplastic autonomic dysfunction discussed here resolved after initiation of AML-directed therapy, demonstrating a unique example where the paraneoplastic sequelae remitted with treatment of the underlying hematologic neoplasm.

## Conclusions

Paraneoplastic autonomic dysfunction has been reported concurrently with other irreversible neurological disorders, which attributes to increased mortality and morbidity complicating the disease course of a primary neoplasm. This patient presented with severe orthostatic hypotension, which resolved after treatment of the leukemia. This report demonstrates that neurological deficits associated with leukemia require immediate attention, and treatment of the hematologic malignancy can reduce the morbidity associated with PNP. Physicians should be aware of this unusual association and not allow delay in treatment of the leukemia.

### Conflict of Interest Statement

There are no conflicts of interest regarding the publication of this article.

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