

Dementia or Depression?

Diagnostic Bias in Geriatric Practice

Gary J. Kennedy, MD, Claudene George, MD, RPh, and Yvonne W. Lui, MD

The distinction between dementia and depression in the care of older adults is a common challenge made more difficult when other illnesses and medications confound the task. Practitioners are subject to biases resulting from the frequency with which they encounter clinical syndromes as well as pride in “making the diagnosis,” particularly when the disease is rare. The following is a case in which one diagnosis was accurately rejected but the correct diagnosis was missed. This affords an opportunity to examine a common clinical problem with an uncommon cause in geriatric practice.

PRESENTATION OF A CASE

An oncologist asked that his formerly high spirited 81-year-old wife and retired teacher be seen for optimization of antidepressant therapy. She was taking fluoxetine 40 mg with little benefit and over the last 2 months had been listless. She had cancer of the breast and now metastatic disease not involving the brain but causing back pain due to metastatic lesions. She had taken steroids and narcotic analgesics but the mental decline preceded both. At the time of evaluation she was taking zolpidem and diphenhydramine on occasion. She denied tearfulness or irritability. Her chief complaint was back pain.

She had a knee replacement and laminectomy in her early seventies with positive results. However, after treatment for breast cancer with radical mastectomy, chemotherapy, and radiotherapy in 2001 she became subdued and tried venlafaxine 37.5 mg. She found it intolerable due to nausea and vomiting and ultimately switched to fluoxetine 20 mg. Her mood

changed little when metastases to her spine and liver were discovered in 2008. Computerized tomography (CT) scans of her brain in 2001 and again in 2008 found no evidence of cerebral involvement. Hospitalized in the spring of 2009, she was found to have atrial fibrillation and adrenal insufficiency. Within 1 month of discharge she developed back pain associated with spinal metastasis. As the pain worsened so did the depression. She received narcotic analgesics, nerve block, and then focused radiotherapy and high dose steroids which were tapered to a minimum. Fluoxetine was increased to 40 mg. Other diagnoses included hypertension, hypothyroidism, hypercholesterolemia, osteoporosis, and epigastric pain. Her medication regimen both on the day of the evaluation and during the preceding month appears in Table 1.

Mental status examination revealed marked psychomotor slowing; euthymic mood; and shallow, silly affect not in keeping with her history nor the gravity of her condition. She could not explain why her back hurt and could not complete the Memory Impairment Screen¹ beyond the registra-

Dr. Kennedy is professor in the Department of Psychiatry and Behavioral Sciences at Albert Einstein College of Medicine, and director of the Division of Geriatric Psychiatry at Montefiore Medical Center in the Bronx, New York. Dr. George is an attending physician in the Division of Geriatric Medicine at Montefiore Medical Center and an assistant professor of Internal Medicine at Albert Einstein College of Medicine. Dr. Lui is an attending physician in the Division of Neuroradiology at Montefiore Medical Center and an assistant professor of Radiology at Albert Einstein College of Medicine.

Disclosure: Dr. Kennedy has received grant support from Forest. Drs. George and Lui report no affiliation with or financial interest in any organization that may pose a conflict of interest.

Please direct all correspondence to: Gary J. Kennedy, MD, Director, Division of Geriatric Psychiatry, Montefiore Medical Center, 111 East 210th St, Bronx, NY 10467; Tel: 718-920-4236; Fax: 718-920-6538; E-mail: gjkennedy@msn.com.

tion phase, which took three trials. She recalled none of the Memory Screen items, could not undertake the Oral Trails-B test of executive function,² and offered only three grocery list items of an expected 20 as a test of semantic memory from the Mattis Dementia Rating Scale.³ Her hearing was impaired (she forgot her hearing aid) but she seemed to understand the tests and gave her best effort. There was no evidence of hallucinations, suicidal ideas, or delusions. However, awareness of her condition was impaired.

DIFFERENTIAL DIAGNOSIS

As shown in Table 2, numerous diagnoses, conditions, and medications could account for her rapid decline. However, she did not display the irritability, apathy, memory complaints, nor characteristic cognitive performance associated with the pseudodementia of a major depressive disorder.⁴ In addition, numerous medications had been administered which could have caused drug-induced delirium or change in mental status due to the Syndrome of Inappropriate Antidiuretic Hormone (vasopressin; SIADH).⁵ However, most medications were either at a stable dose, had been tapered to a minimum dose, or were used sporadically excepting fluoxetine which had been increased. Moreover, the signs and symptoms of SIADH, save difficulty concentrating and memory impairment, were absent.⁶ A space occupying lesion in the brain could account for the severity of cognitive decline

but had not been detected on the last brain imaging study in 2008. More consistent with the sudden decline in multiple cognitive domains was rapidly progressive dementia due to a distant or indirect effect of the breast cancer, raising the possibility of a paraneoplastic neurologic syndrome.^{7,8}

TREATMENT PLAN AND OUTCOME

The provisional treatment plan included tapering and then discontinuing the fluoxetine, forgoing subsequent doses of diphenhydramine, adding bupropion 100 mg for its stimulating effect, and proceeding as though the antidepressant had failed. However, the alternative diagnosis was paraneoplastic syndrome “due to the cancer,” and if correct, an antidepressant would have little benefit. The patient was unfazed by the caveat but the husband was visibly distressed. Both agreed to return in 2 weeks for a reassessment. However, shortly after beginning the bupropion she was hospitalized for “confusion, change in mental status, [and] weakness in the lower extremities.” CT scan of the brain at that time demonstrated no sign of intracranial metastasis and no findings characteristic of central nervous system (CNS) paraneoplastic syndromes including limbic encephalitis, an entity that can present with mental status changes and dementia. The patient’s serum osmolality was low at 239 mOsm/kg in the context of normal urine osmolality (541 mOsm/kg); serum sodium was 119

TABLE 1
MEDICATION REGIMEN

At the time of the psychiatric evaluation

- Cortef (hydrocortisone) 10 mg TID
- Decadron (dexamethasone) 2 mg/day
- Amiodarone 200 mg/day
- Cozaar (losartan) 50 mg BID
- Hydrochlorothiazide 12.5 mg/day
- Omeprazole 20 mg BID
- Pepcid (famotidine) 20 mg PRN
- Levothyroxine 100 mcg
- Fluoxetine 40 mg/day
- Oxycodone 15 mg PRN
- Ambien (zolpidem) 10 mg HS
- Benadryl (Diphenhydramine) PRN
- Calcium/Vitamin D, Beta carotene, folic acid, zinc, omega fish oil

In the month prior to the evaluation

- Oxycodone 15 mg PRN
- Methylprednisolone 60 mg, then 30 mg, then 0 mg
- Decadron (Dexamethasone) 16 mg to 2 mg
- Fluoxetine 20 mg/day

Kennedy GJ, George C, Lui YW. *Primary Psychiatry*. Vol 16, No 10. 2009.

TABLE 2
POTENTIAL CAUSES OF RAPID COGNITIVE DECLINE IN AN 81-YEAR-OLD WOMAN WITH METASTATIC BREAST CANCER AND A HISTORY OF DEPRESSION

Exacerbation of depression (pseudodementia)

- Irritability, apathy
- Refusal to undertake cognitive testing
- Explicit complaints of memory impairment without evidence of executive dysfunction, anomia, or aphasia

Medications

- Delirium due to diphenhydramine, zolpidem, oxycodone, fluoxetine
- Syndrome of Inappropriate antidiuretic hormone due to fluoxetine, omeprazole, or hydrochlorothiazide
 - Headache
 - Difficulty concentrating, impaired memory
 - Nausea, vomiting, weakness
 - Muscle cramps, seizures
 - Hyponatremia with euvolemia
 - Hypo-osmolality of serum, increased urine osmolality

Metastases to the brain

Dementia, paraneoplastic syndrome

Kennedy GJ, George C, Lui YW. *Primary Psychiatry*. Vol 16, No 10. 2009.

mEq/L and serum chloride was 80 mEq/L, both abnormally low. Other laboratory examinations were unremarkable and her physical exam had changed little from the previous month. She was treated for SIADH by fluid restriction and discontinuation of bupropion and fluoxetine. Her mood did not change but was now better characterized by resignation and frustration than depression, and she was discharged home. She was less confused and did not feel the need for subsequent psychiatric care.

DISCUSSION

The paraneoplastic neurologic disorders are syndromes that occur in the setting of primary neoplasm. They are related to an immunologic response in which antibodies to tumor cells cross-react with healthy tissue, attract cytotoxic cells, and lead to organ damage. Though these syndromes are rare, they are important to consider because they are potentially reversible. Paraneoplastic neurologic conditions can affect various parts of the CNS and peripheral nervous system. Perhaps the best defined immunologic relationship has been established with the Lambert-Eaton syndrome in which antibodies to the neuromuscular junction can cause myasthenia-type syndrome. Paraneoplastic syndromes associated with the CNS are listed in Table 3.⁸ Several syndromes may manifest as rapidly progressive but potentially reversible dementia provided the primary tumor is treated.

Although SIADH may be drug induced, it may also be an endocrine paraneoplastic syndrome which is believed to have a non-immunologic mechanism. Nevertheless, this is an important entity to consider in the setting of changes in men-

tal status as the syndrome may present primarily as cognitive dysfunction and behavioral abnormalities. Paraneoplastic SIADH is believed to result from ectopic production of vasopressin by the primary tumor. Again, treating the tumor resolves the syndrome.

Medication-induced SIADH, although uncommon, is far more frequently encountered than the paraneoplastic SIADH. And serotonergic antidepressants as well as hydrochlorothiazide and omeprazole can induce the syndrome, further suggesting the diagnosis in this case. The mechanism of selective serotonin reuptake inhibitor (SSRI)-induced SIADH is unclear. Serotonin-mediated effects on 5-HT₂ and 5-HT_{1C} receptors are associated with vasopressin release. Some SSRIs also inhibit norepinephrine reuptake, which may induce vasopressin release by stimulating α_1 adrenergic receptors. SIADH may also be a manifestation of drug-drug interactions. Fluoxetine in particular inhibits a number of cytochrome P450 isoenzymes and may potentiate the hyponatremic effects of other medications.⁵ In addition, older adults are at greater risk for drug-induced SIADH just as they are for the confusional effects of steroids, narcotic analgesics, sedative antihistamines, and hypnotics.

To understand how the psychiatrist's diagnostic choice was skewed correctly away from depression but incorrectly toward the less probable paraneoplastic syndrome, it may be helpful to examine sources of bias related to the character of the individual's practice. Here the psychiatrist (GJK) practices in an academic medical center division of geriatric psychiatry in which few patients with depression are referred for initiation of antidepressant therapy. Most have been exposed to an SSRI prior to referral so that SIADH is more likely to emerge in the referring physician's practice rather than in the consultant's. Further, because the consultant's practice is limited to geriatric patients, there is a substantial prevalence of dementia. People whose dementia is not complicated by behavioral disturbances or the family's need for counseling are rarely referred unless the presentation is atypical or the diagnosis is uncertain. As a result, the psychiatrist had once correctly diagnosed dementia due to a paraneoplastic syndrome but never SIADH despite having encountered cases in teaching rounds. Jerome Gropman⁹ argues that physicians tend to diagnose the next patient based on how they diagnosed of the last patient. Past experience influences future behavior. This is often to the advantage of the patient and physician in that diagnostic sensitivity and therapeutic efficiency are enhanced. However, diagnostic specificity and therefore definitive treatment may suffer as a result.

TABLE 3

PARANEOPLASTIC SYNDROMES AFFECTING THE CENTRAL NERVOUS SYSTEM⁸

Limbic encephalitis
Brain-stem encephalitis
Cerebellar degeneration
Opsoclonus-myoclonus
Cancer-associated retinopathy
Optic neuritis
Chorea
Parkinsonism

Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med*. 2003;349(16):1543-1554. Adapted with permission from the Massachusetts Medical Society. Copyright 2003.

Kennedy GJ, George C, Lui YW. *Primary Psychiatry*. Vol 16, No 10. 2009.

CONCLUSION

In this example, the diagnosis of depression was rightly rejected and a cognitive disorder was chosen. Based only on the prevalence of dementia in the physician's practice the probabilities favored a cognitive disorder. However, prior experience with one case of paraneoplastic syndrome and the extent of the patient's cancer tipped the balance toward dementia rather than drug-induced SIADH. The appeal of making an exotic, rare diagnosis also may have biased the decision. Stopping the fluoxetine and starting the non-serotonergic agent bupropion for possible depression made sense, but a better choice would have included simple laboratory studies to search for a reversible cause of rapid cognitive decline. Identifying hyponatremia and

instituting fluid restriction might have avoided the subsequent hospitalization. **PP**

REFERENCES

1. Grober E, Hall C, McGinn M, et al. Neuropsychological strategies for detecting early dementia. *J Int Neuropsychol Soc.* 2008;14(1):130-142.
2. Ricker JH, Axelrod BN. Analysis of an oral paradigm for the trail making test. *Assessment.* 1994;1(1):47-51.
3. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Kerasu TB, eds. *Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians.* New York, NY: Grune and Stratton; 1976:79-121.
4. Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry.* 1993;150(11):1693-1699.
5. Guay DR. Hyponatremia associated with selective serotonin reuptake inhibitors: clinical review. *Consult Pharm.* 2000;15:160-177.
6. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med.* 2007;356(20):2064-2072.
7. Sabin TD, Jednacz JA, Staats PN. Case records of the Massachusetts General Hospital. Case 26-2008. A 26-year-old woman with headache and behavioral changes. *N Engl J Med.* 2008;359(8):842-853.
8. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med.* 2003;349(16):1543-1554.
9. Gropman J. *How Doctors Think.* New York, NY: Houghton Mifflin; 2007.