CASE REPORT & REVIEW

Paraneoplastic Limbic Encephalitis: Neuropsychiatric Presentation

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Limbic encephalitis as a distinct clinicopathological entity is becoming increasingly familiar to neurologists. However, despite its classical clinical presentation of mental status changes and behavioral abnormalities, the disorder is not well known in the psychiatric literature and premortem diagnosis is rare. We recently participated in the care of a patient who spent two months on a psychiatric service and in whom a medical disorder was consistently suspected but not confirmed until autopsy revealed paraneoplastic limbic encephalitis and two primary systemic malignancies. A detailed neuropsychiatric description of this clinical entity is provided from presentation to autopsy with review of the literature.

Introduction

Clinical data have repeatedly illustrated the need for psychiatrists—especially geriatric psychiatrists—to include etiologically relevant medical disorders in psychiatric differential diagnoses (Hall et al. 1978; Hall et al. 1980; Jenicke 1985; Maricle et al. 1987). Apparent psychosocial precipitants can sometimes lead to an erroneous or incomplete functional diagnosis when a more complex psychobiological etiology may be involved. This article presents a case report and review of the literature on one such syndrome, paraneoplastic limbic encephalitis.

Case Report

The patient was a 76-year-old white married man, a retired typesetter, who was transferred from his local community hospital to the McLean Hospital Geriatric Inpatient Service for his first psychiatric admission. His chief complaint was "I'm feeling low, but I've been healthy all my life." Five weeks earlier, he experienced sudden-onset amnesia following the death of his brother. This was first noticed during the funeral, when he appeared confused, needed help orienting himself, and exhibited no memory of his

brother's death. On initial admission to a community hospital for medical/neurological evaluation, he was ambulatory and able to perform activities of daily living, but was confused, and had poor short-term memory. Evaluation revealed no specific medical etiology for his memory problems; routine laboratory tests, thyroid function studies, carotid noninvasive studies, and liver-spleen scan were normal. Cerebrospinal fluid (CSF) was clear and colorless with a glucose of 91 mg%, protein of 54 mg%, and 7% lymphocytes. Electroencephalogram (EEG) was normal. Brain scans by computer-assisted tomography (CT) and magnetic resonance imaging (MRI) revealed asymmetric dilation of the left lateral ventricle.

Behaviorally, he exhibited marked deterioration while in the community hospital, with day-night reversal and increasing nocturnal agitation. He became unable to feed or care for himself without constant supervision, struck out at staff, and tried to climb out of bed. Trials of several tranquilizers and sedatives were attempted, including haloperidol (up to 120 mg on 1 day), chlorpromazine, chloral hydrate, nembutal, lorazepam, and thioridazine. He suffered a 45-sec period of apnea that was presumed to be secondary to the drugs. Differential diagnoses ranged from Alzheimer's disease to Korsakoff's syndrome, from major depression to psychogenic amnesia.

The patient had no prior psychiatric illness and no history of substance abuse, head trauma, or seizures. He had smoked in the past. Family history was significant for past alcoholism in one brother and a 3-day amnestic episode after the death of a relative in another brother.

On transfer to McLean Hospital, he was unable to stand or walk without support, and his gait was described as "rubbery." He was cooperative but oriented only to person. Speech was slow and monotonous. Mood and affect appeared depressed. Thought process was without tangentiality or looseness. Thought content revealed no delusions. He denied suicidal or homicidal ideation. He showed no evidence of auditory or visual hallucinations or illusions. On cognitive testing he could name objects but remembered none of the three objects after 3 min. He was unable to name the president or his own wife. He promptly forgot that his brother had died after he was reminded of the event during the admission interview. He was unaware that he was in the hospital.

Admission laboratory studies revealed an elevated white blood cell count (WBC) of 11,700 and Wintrobe sedimentation rate of 17 mm/hr. Urinalysis, serologic test for syphilis, blood cultures, blood gases, ammonia, and carcinoembryonic antigen were normal; thyroid studies showed elevated T3 uptake at 41%. Alkaline phosphatase was elevated on admission at 124 U/liter, but returned to normal within 3 weeks. Dexamethasone suppression test (1 mg) performed 2 weeks after McLean admission was abnormal, with a 4 PM baseline cortisol of 21.1 μg/dl and 4 PM postdexamethasone cortisol of 25.2 μg/dl. Chest x-ray films at admission and 6 weeks later both showed clear lungs. Noncontrast CT scan revealed a dilated left lateral ventrical and atrophy of the right inferofrontal and left parietal cortex. Lumbar puncture showed an opening pressure of 150 mm water, closing pressure of 120 mm water, with a WBC of 8 (50% lymphocytes and 50% monocytes), glucose 68 mg%, protein 60 mg%, and negative cultures. EEG demonstrated mild abnormality due to persistent background theta slowing.

After initial psychiatric evaluation, hypotheses included a toxic syndrome secondary to high doses of neuroleptics or a residuum of neuroleptic malignant syndrome. However, the patient had a normal admission creatine phosphokinase, and, despite several weeks without neuroleptics, there was no change in his condition. He was always disoriented to place, date, and time, usually lethargic and somnolent, difficult to arouse during the

day and more agitated in the early-to-late evening. He did not always recognize his wife, although he spoke fondly of her to staff. At times he complained of a frontal headache and said he did not feel well.

On neurological examinations repeated 12 days and 36 days after admission, short-term memory remained poor; long-term memory was more variable. He showed no evidence of confabulation. He could count backwards from 10 to 1 but could not do serial 3 subtractions. He could follow a two-step command and perform a heel to shin maneuver without error while in bed. He had frontal release signs including pathological grasp reflexes. There were no demonstrable motor or sensory deficits.

He underwent successive individual drug trials with lorazepam, clonazepam, benztropine, diphenhydramine, lithium, thiothixene, and low-dose haloperidol with minimal effect on his agitation. His persistent problems of extreme daytime somnolence and episodic hypotension (70–90/palle) even without medications limited pharmacological options. He also exhibited hypothermia throughout his hospitalization, and the usual diurnal variation in temperature was reversed (e.g., 9 AM mean = 97.6°F; 4 PM = 97.1°F). He required brief interim transfer to a medical hospital for bilateral pneumonia and a subsequent urinary tract infection, both successfully treated with antibiotics.

Two months after his McLean admission, he was discharged home in the care of his wife and home health aides. Axis I discharges diagnoses were chronic, unspecified organic brain syndrome and status postdelirium secondary to pneumonia and urinary tract infection. His agitation, however, was unmanageable, and within a few days he was admitted to the medical service at Massachusetts General Hospital.

At that time, a neurological evaluation revealed orientation only to person and 0/3 recall at 5 min, but intact reading, writing, repetition, naming, comprehension, praxis, and simple calculations. There was slight left ptosis and anisocoria consistent with a left Horner's syndrome, left-beating horizontal nystagmus on left lateral gaze, a skew deviation with left eye deviated up and out, and a flattened right nasolabial fold, all suggesting brainstem involvement. Motor, cerebellar, and sensation functions were intact. Deep tendon reflexes were symmetric, toes flexor, and a snout reflex present. Chest radiograph revealed patchy bibasilar infiltrates.

EEG showed bursts of left temporal sharp slowing superimposed on an abnormally slow background. A subsequent phenytoin trial for possible complex partial seizure activity had no clinical effect. His behavioral abnormalities persisted despite discontinuation of psychotropic medications. He developed cardiac failure, pneumonia, dyspnea, and cystitis with severe protracted hypotension (80/40), but no fever. He died 4 months after the onset of his memory problems. There was no clinical evidence of systemic malignancy.

On autopsy, the brain weighed 1200 g. There was moderate atrophy of the frontal and superior temporal lobes and moderate dilatation of the lateral and third ventricles. The hippocampal formation was markedly shrunken and discolored bilaterally throughout the entire anteroposterior extent (Figure 1).

On microscopic inspection, there was diffuse cortical gliosis of anterior cingulate, insular, posterior superior parietal, and temporal cortices. The gliosis was most severe in the temporal lobe, particularly in the amygdala, periamygdaloidal cortex, and hippocampal formation. Intense perivascular inflammation and scattered microglial nodules accompanied the gliosis. Perivascular inflammatory cuffs consisted of lymphocytes admixed with plasma cells and rare mononuclear cells (Figure 2). There was severe neuronal loss in the hippocampal formation with virtually complete absence of pyramidal neurons

Figure 1. Photograph shows atrophy, severe neuronal loss, and gliosis in the hippocampal formation, most prominent in the pyramidal cell layers of Ammon's horn (arrowhead) (hematoxylin and eosin, original magnification × 5).

in Ammon's horn and moderate neuronal loss in the subiculum. Astrocytosis and perivascular inflammation were found in the mammillary bodies and substantia innominata, but the septal region, basal ganglia, thalamus, and hypothalamus were otherwise unaffected.

Although the limbic system was primarily damaged, there were lesions in the pons and medulla with microglial proliferation, perivascular inflammation, and neuronophagia consistent with a more acute phase in the pathological process. The midbrain, cerebellum, spinal cord, dorsal and motor roots, dorsal root ganglia, and cranial nerves were unaffected.

General pathological examination revealed small cell (oat cell) carcinoma of the left lingula with metastases to hilar lymph nodes, and renal cell carcinoma with invasion of renal veins. There was no other gross evidence of either small cell or renal cell carcinoma metastases. Anatomical diagnosis was paraneoplastic limbic encephalitis.

Discussion

The paraneoplastic syndromes constitute a diverse group of illnesses affecting a wide range of organ systems (Mendelsohn 1987). By definition, they reflect the remote effects of cancer rather than direct effects such as metastatic invasion of tissues or other, nonmetastatic consequences of systemic malignancy including metabolic and/or nutritional abnormalities, infectious or ischemic complications, or side effects of therapy.

In the nervous system, these syndromes are relatively rare and must be primarily differentiated from local intracranial, spinal, leptomeningeal, or peripheral nerve metastatic involvement (Patchell and Posner 1985; Anderson and Posner 1987). Approximately 15%–20% of all patients with systemic malignancy may have neurological symptoms at
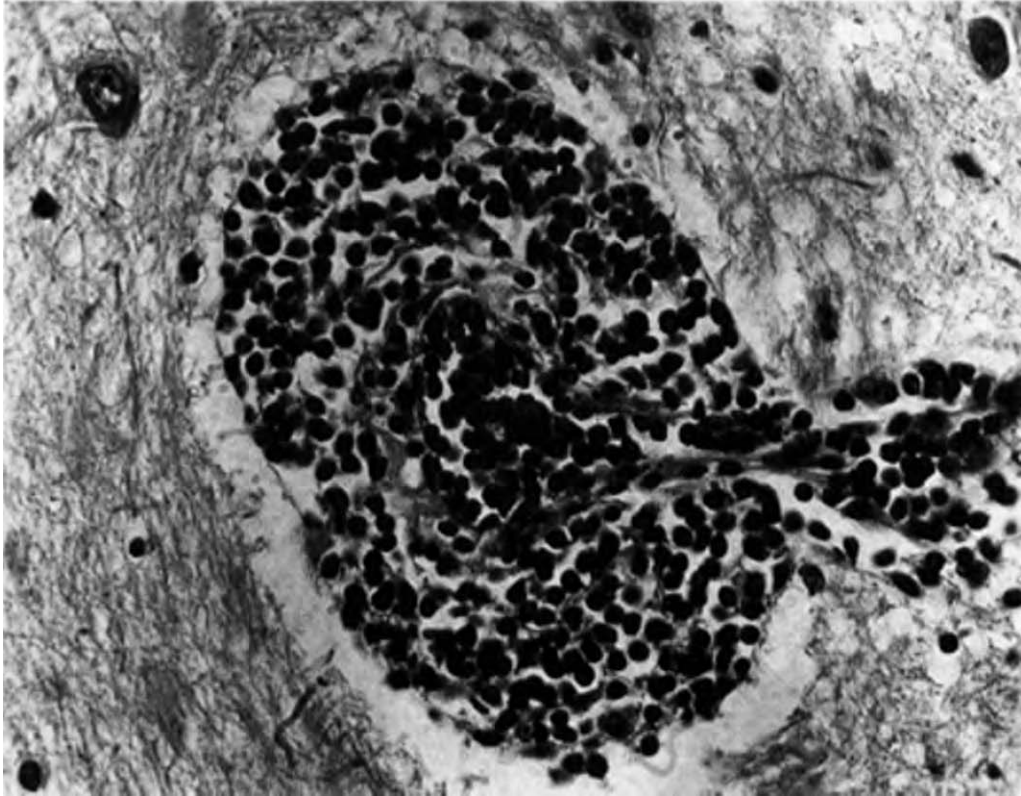
Figure 2. Photo shows small vein in the amygdala surrounded by a dense accumulation of lymphocytes and occasional plasma cells (hematoxylin and eosin, original magnification × 230).

some point in their clinical course, 10% of the neurological morbidity deriving from paraneoplastic syndromes (Henson and Urich 1982; Palma 1985). The highest incidence with paraneoplastic neurological disorders is in patients with carcinoma of the lung and ovary (Henson and Urich 1982; Anderson and Posner 1987). These symptoms may appear before systemic evidence of malignancy in as many as half of the patients (Anderson and Posner 1987). Frequently the neurological manifestations are debilitating in their own right.

Almost all regions of the nervous system are susceptible to a paraneoplastic process, including muscle, neuromuscular junction, root and peripheral nerve, spinal cord, brainstem, cerebellum, and cerebral hemispheres (Henson and Urich 1982; Stefansson and Arnason 1987). Frequently multiple neuroanatomical regions are involved clinically or pathologically. Certain cancer types tend to be associated more frequently with specific anatomical sites (Henson and Urich 1981; Palma 1985; Stefansson and Arnason 1987). However, every syndrome has been noted, in either individual case reports or small series, to occur in patients without systemic cancer manifested in life or on autopsy (Langston et al. 1975; Dubas et al. 1982b; Henson and Urich 1982; Daniel et al. 1985; Palma 1985; Stefansson and Arnason 1987).

Limbic Encephalitis: Historical Overview

Limbic encephalitis was first elaborated upon by Brierly et al. (1960) as a distinct clincopathological entity, based on pathological study of 3 patients and review of case reports from the 1950s by Greenfield and others. Henson et al. (1965) remarked on the frequent

association of encephalomyelitis with systemic carcinoma. This was amplified 3 years later by Corsellis et al. (1968), who stressed the connection between pathological involvement of the gray matter of the limbic system and clinically predominant signs of memory loss and dementia. Subsequently, this syndrome was clarified and expanded, and the literature was reviewed by Henson and Urich (1982), Dubas et al. (1982a, 1982b), Glaser and Pincus (1969), Dorfman and Forno (1972), Kaplan and Itabishi (1974), Palma (1985), Richardson (1985), and Anderson and Posner (1987).

Pathology

The pathology is frequently striking in its extent of destruction and its anatomic specificity. The exact anatomic boundaries of the limbic system are still a matter of some debate; physiological and molecular studies constantly redefine what constitutes a functional system within the brain (Levitt et al. 1986). Over 100 years ago, Broca (1878) first described the anatomically unified deep brain structures considered to be the core of the limbic system, and 50 years later, Papez (1937) suggested that this region was essential for human emotions. The main areas include the hippocampus, amygdala and other mesial temporal lobe structures, insula, cingulate gyrus, pyriform cortex, orbital surface of the frontal lobe, hypothalamus, and occasionally, portions of basal ganglia structures. Animal studies and observations in humans with anatomically localized disease further support the widely held view that the limbic system plays a central role in emotional and affective display and memory, as well as in various aspects of hormonal and visceral control (Himmelhoch et al. 1970; Torrey and Peterson 1974; Koella 1984; Isaacson 1982; Cornelius et al. 1986).

The gross pathology of limbic encephalitis is usually without significant abnormalities. Occasionally there is atrophy of the hippocampi and/or mild dilatation of the inferior horns of the lateral ventricles (Brierly et al. 1960; Henson et al. 1965; Corsellis et al. 1968; Henson and Urich 1982). Microscopically, however, extensive neuronal loss with reactive gliosis, perivascular monocytic infiltrates, and microglial nodules are seen.

Limbic encephalitis is rarely found in isolation. Often characteristic pathological findings and clinical symptomatology are noted in at least one other anatomical region, specifically the brainstem, spinal cord, or dorsal root ganglia (Brierly et al. 1960; Henson et al. 1965; Corsellis et al. 1968; Dubas et al. 1982a; Dubas et al. 1982b; Henson and Urich 1982; Richardson 1985).

Clinical Presentation

The clinical presentation of limbic encephalitis has been outlined in over 40 published case histories and summarized in several brief reviews (Brierly et al. 1960; Henson et al. 1965; Corsellis et al. 1968; Glaser and Pincus 1969; Dorfman and Forno, 1972; Kaplan and Itabishi 1974; Langston et al. 1975; Henson and Urich 1982; Dubas et al. 1982a; Dubas et al. 1982b; Daniel et al. 1985; Palma 1985; Richardson 1985; Cornelius et al. 1986; Anderson and Posner 1987; Camera and Chelune 1987; Franck et al. 1987; Stefansson and Arnason 1987; Tandon et al. 1988) (Table 1). There is approximately equal frequency of both genders, and age of onset is between 50–70 years old (range 39–80). Onset can be insidious, but is frequently dramatic, with prominent changes in the baseline mental status. Affective symptoms and striking difficulties with memory remain the core features. There are usually elements of depression and/or anxiety, personality changes,

agitation, hallucinations, distortion of perceptions, paranoia, feelings of depersonaliza-
tion, and bizarre behavior. Memory, both short and long term, is significantly impaired,
whereas other cognitive functions remain relatively intact.

In light of this predominantly behavioral and affective presentation, it is not surprising
that the majority of these patients undergo psychiatric evaluation and even hospitalization.
A review of the available case histories in the literature of pathologically proven limbic
encephalitis reveals—of a total of 39 cases—only 3 who did not present with prominent
mental status abnormalities (Henson et al. 1965; Dubas et al. 1982a; Dubas et al. 1982b).
Indeed, when information is provided on type of initial hospitalization, 10 of 19 patients
were admitted to psychiatric services and treated with psychotropic medications and even
electroconvulsive therapy (Brierly et al. 1960; Glaser and Pincus 1969; Himmelhoch et
al. 1970; Dubas et al. 1982a; Dubas et al. 1982b; Richardson 1985; Cornelius et al.
1986; Camara and Chelune 1987; Tandon et al. 1988). However, the history, especially
the rapidity of onset in the middle-aged to elderly patient without previous psychiatric
difficulties, combined with formal mental status testing, may suggest an underlying
medical etiology.

General and neurological examinations (apart from mental status testing) may be
entirely normal. Detailed neurological evaluation, however, may reveal subtle asym-
metries or brainstem, spinal cord, cerebellar, or peripheral nerve abnormalities reflecting
involvement of another portion of the nervous system. Later in the course, seizures, both
psychomotor and grand mal, have been reported. CT and MRI studies are usually with
normal limits. EEGs may be normal early in the clinical course, but eventually show
nonspecific abnormalities such as generalized background slowing, occasionally with
superimposed unilateral or bilateral temporal slow waves and/or spike foci. Lumbar
punctures reveal normal opening and closing pressures, normal CSF glucose levels, an
elevated protein (greater than 45 mg%) in approximately 75% (range = normal to 480,
mean = 87), and a mononuclear predominant pleocytosis in approximately 60% of cases
(range = 0–146, mean = 30).

The course is typically subacute with worsening over weeks or months. Fluctuations
have been reported, but no spontaneous remissions, and the course is generally progres-
sive. Survival from presentation until death ranges from 1 to 22 months. Initial differential
diagnosis includes the infectious encephalitides (especially viral, the slow virus of subacute
spongiform encephalopathy, and Whipple's disease), metabolic disorders, Korsakoff's
syndrome, degenerative dementias, bilateral infarctions, central nervous system vasculitis,
systemic lupus erythematosus, and cerebral metastases.

On autopsy, the associated malignancy is usually oat cell carcinoma of the lung,
but primary malignancies in ovary, breast, stomach, uterus, kidney, and colon have
been reported (Brierly et al. 1960; Henson et al. 1965; Corsellis et al. 1968; Himmel-
hoch et al. 1970; Dorfman and Forno 1972; Kaplan and Itabishi 1974; Dubas et al.
1982a, 1982b; Henson and Urich 1982; Richardson 1985; Cornelius et al. 1986; An-
derson and Posner 1987; Camara and Chelune 1987; Franck et al. 1987; Janati et al.
1987; Tandon et al. 1988). It has been suggested that a similar syndrome can occur
with the recurrence of Hodgkin's disease (Carr 1982), but there have been no patho-
logically proven cases. The identical clinical and pathological syndrome has also been
noted in the absence of cancer on general necropsy (Himmelhoch et al. 1970; Langs-
ton et al. 1975; Dubas et al. 1982b; Delsedime et al. 1984; Daniel et al. 1985). No
distinction among underlying tumor pathologies can be made based on the clinical pre-
sentation of this paraneoplastic syndrome.

Table 1. Reported Cases of Pathology-Confirmed Limbic Encephalitis

Author	Case #	Age/Gender	Prominent mental status change	Psych Dx	Time from presentation to death	1° CA	CSF evaluation White cells	CSF evaluation Protein	Other
Brierly et al. 1960	1	55 M	Yes	Yes	14 mo	None	"Normal"	"Normal"	EEG abnormal
	2	58 M	Yes	Yes	2½ mo	Lung	24,146	90,100	
	3	56 M	Yes	No	7 mo	None	37,28,12	90,70,30	EEG abnormal Seizures
Verhaart 1961		51 M	Yes	No	8 mo	Lung	40	138	
Storring 1962		49 M	Yes	NA	12 mo	Lung	125	53	
Henson et al. 1965	1	39 F	No	No	13 mo	Uterus	4,1,3	174,480,161	
	6	53 M	Yes	NA	17 mo	Lung	NA		
	7	61 F	Yes	NA	20 mo	Lang	NA		
	8	73 F	Yes	NA	6 mo	Breast	NA		
Yahr 1965		61 F	Yes	NA	13 mo	Lung	0	71,54	EEG abnormal
Ulrich 1967		58 M	Yes	NA	16 mo	Lung	21	59	EEG abnormal
Marsal 1967		56 M	No	NA	10 mo	None	0	10	
Corsellis et al. 1968	1	60 M	Yes	No	22 mo	Lung	2	25	EEG abnormal
	2	50 M	Yes	NA	20 mo	Lung	"Normal"	"Normal"	EEG abnormal
	3	80 F	Yes	NA	1-2 yrs	Lung	NA		
Julien 1969	28	42 M	No	NA	16 mo	Stomach	50	250	
Vick 1969	29	62 M	Yes	NA	6 mo	Lung	10	130	
Glaser and Pincus 1969	1	56 F	Yes	Yes	3 mo	Lung	0	95	EEG abnormal
Himmelhoch et al. 1970	2	47 F	Yes	Yes	8 mo	None	11	90	EEG abnormal
Arne 1970	30	62 M	Yes	NA	4 mo	Lung	27	50	
Spalke 1971	31/1	54 M	Yes	NA	12 mo	Lung	93	100	
Kaplan and Itabishi 1974	32/2	59 F	Yes	NA	18 mo	Ovary	11	50	
	37	61 M	Yes	No	15 mo	Lung	3	88	EEG abnormal
Langston et al. 1975		66 M	Yes	No	13 mo	None	32	143,228	EEG abnormal

Reference	Case	Age/Sex	Psych DX		Duration	Tumor	CSF cells	CSF protein	Findings
Sarbach 1977	38	77 M	Yes	NA	11 mo	Lung		"Normal"	EEG abnormal
Muller 1978	40	79 M	Yes	NA	NA	Lung		NA	EEG abnormal
Dubas et al. 1982 (a)	I	53 M	Yes	No	12 mo	Lung	26	100	EEG abnormal
	III	51 M	Yes	Yes	10 mo	Kidney	NA		EEG abnormal
	VI	76 M	Yes	NA	5 mo	Lung	3	50	CT normal
Dubas et al. 1982 (b)	I	64 F	Yes	NA	1 mo	None	40	75	EEG abnormal
	II	79 M	Yes	NA	3 mo	None	34	170	CT normal
	IV	59 M	Yes	No	1 mo	None	32	135	EEG mildly abnormal; Seizures; CT normal
Richardson 1985		52 F	Yes	Yes	1 yr	Bladder	8–20	20–47	Seizures; EEG abnormal
Daniel et al. 1985	3	61 F	Yes	NA	2 mo	None	NA	"Normal"	EEG abnormal; Seizures; CT normal
Cornelius et al. 1986		66 M	Yes	Yes	4 mo	Lung	87	65	EEG normal; CT normal; MRI normal
Camara and Chelune 1987		61 F	Yes	Yes	2 yrs	Lung		"Negative"	SIADH; Seizures
Franck et al. 1987		55 M	Yes	No	22 mo	Lung		"Normal"	EEG abnormal; PET abnormal; CT normal
Tandon et al. 1988		58 F	Yes	Yes	NA	Lung	NA	70	CT normal; EEG abnormal
Newman et al. 1988		76 M	Yes	Yes	4½ mo	Lung, kidney	7,8	54,60	EEG abnormal; CT normal; MRI normal

Psych DX = patient received an initial "psychiatric" diagnosis (see text).
M = male, F = female, NA = information not available.
CSF: cells = number of leukocytes/cu mm, protein = mg/100 mL.
SIADH = syndrome of inappropriate antidiuretic hormone.

Etiological Theories

The etiology of limbic encephalitis remains unknown. In several other paraneoplastic syndromes of the nervous system, a causal agent or a pathophysiological mechanism has been strongly suspected or proven to exist: for example, progressive multifocal leuken-cephalopathy due to JC papova virus (no longer considered a paraneoplastic syndrome once the etiological agent was discovered); Eaton-Lambert syndrome secondary to an-tibodies directed against components of the presynaptic membrane of the neuromuscular junction; cerebellar degeneration linked with anti-Purkinje cell antibodies (raising the question of common tumor cell and cerebellar antigens and a resultant autoimmune pathology); and paraneoplastic sensory neuropathy associated with antisensory neuronal antibodies (Lang et al. 1981; Jaeckle et al. 1985; Palma 1985; Graus et al. 1986; Greenlee and Lipton 1986; Anderson and Posner 1987).

Similar etiologies have been proposed for limbic encephalitis, the first involving direct viral infection. The pathology suggests an infective etiology, and 2 cases have been reported to exhibit intranuclear (Himmelhoch et al. 1970) and intracytoplasmic (Kaplan and Itabishi 1974) inclusion bodies; however, no viral particles have ever been isolated. Lavi et al. (1988) have described a mouse model of viral-induced encephalitis, anatom-ically restricted to the limbic system and its connections, produced by intranasal inocu-lation of a coronavirus into mice. Intracerebral inoculation of Borna virus in rats and primates produces a clinicopathological entity very similar to human limbic encephalitis (Sprankel et al. 1978; Narayan et al. 1983; Ludwig et al. 1988). Interestingly, Borna virus may play an etiological role in affective disorders, as suggested by the increased incidence of Borna virus-specific antibodies in patients with bipolar and unipolar depres-sion (Amsterdam et al. 1985; Rott et al. 1985; Ludwig et al. 1988).

The immune-mediated theory suggests either tumor/limbic system antigen cross-reac-tivity or an underlying host autoimmune disorder. The latter might explain why some cases show no systemic malignancy on autopsy; they could be either idiopathic or sec-ondary to viral transformation of the immune system. Of relevance to this theory is the recent generation of a monoclonal antibody in rats that recognizes an antigen or antigens specific to neurons of the limbic system (Levitt 1984; Levitt et al. 1986). Recently, 3 patients with clinical limbic encephalitis were reported whose serum contained antineu-ronal IgG antibodies that bound in vitro to neuronal nuclei of cerebral cortex, hippocam-pus, brainstem, and dorsal and anterior horns and to cerebellar granular, Purkinje, basket, and stellate cells (Jaeckle et al. 1988). All 3 cases had concurrent, paraneoplastic clinical involvement in the peripheral nervous system (1 motor neuronopathy, 2 sensory neurop-athies). In 1 patient, plasmapheresis resulted in clinical improvement peripherally, with simultaneous reduction in the antineuronal antibody titer.

In the present patient, one might speculate that the psychological loss of his brother precipitated immune compromise, as has been reported in bereavement (Bartrop et al. 1977; Schleifer et al. 1983). However, bereavement is unlikely as a primary factor because of the immediate onset of his symptoms at the funeral. Previous studies suggest a lag period of 4–8 weeks between the loss and the development of immune impairments (Bartrop et al. 1977; Schleifer et al. 1983).

Treatment

Treatment of the paraneoplastic syndromes becomes an increasingly important issue as patients survive longer and more comfortably due to more successful therapies against

the primary malignancy. Until the etiology of limbic encephalitis is clarified, the options are direct treatment of the underlying cancer and symptomatic treatment of the psychiatric manifestations. Supporting this approach are reports of treatment of malignancy reversing remote effects of certain systemic paraneoplastic syndromes such as Trousseau's syndrome with adenocarcinoma, hypertrophic pulmonary osteoarthropathy and lung cancer, syndrome of inappropriate antidiuretic hormone (SIADH) and oat cell carcinoma, nephrotic syndrome and the lymphomas, and dermatomyositis and its associated malignancies (Markman 1986; Anderson and Posner 1987). Less frequent are the reports of improvement of the primarily neurological paraneoplastic syndromes. However, case reports and small series do exist, particularly with the Eaton-Lambert syndrome due to small cell carcinoma, and with certain neuropathies and neuromyopathies associated with surgically excisable tumors (Markman 1986; Anderson and Posner 1987).

Perhaps the lack of plasticity of the adult central nervous system—its known poor regenerative reserve—makes the reversal of limbic encephalitis a rare occurrence (Greco 1986; Markman 1986). There are 2 reported cases of clinical limbic encephalitis with known oat cell carcinoma in which there was documented clinical improvement following systemic chemotherapy and radiation therapy (in 1 case, directed at the chest; in the other, at the chest and cranium) (Markman and Abeloff 1982; Brennan and Craddock 1983). Memory loss, personality changes, and hallucinations in a 16-year-old with Hodgkin's disease were entirely reversed with treatment of the lymphoma (Carr 1982). In a case of clinical limbic encephalitis secondary to an adenocarcinoma of the colon, cognition was not restored despite improvement in mood, behavior, and appetite after surgical removal of the cancer (Janati et al. 1987). Although there is no pathological verification of limbic encephalitis in these 4 cases, the indication that therapy of the primary malignancy might reverse a syndrome that is highly disabling in its own right has important implications. This is true for both etiology and for early recognition and diagnosis of the syndrome as a marker of an occult but potentially treatable neoplasm.

In conclusion, this patient's case demonstrated a puzzling, precipitous course that suggested an underlying medical disorder despite the lack of definite diagnosis during life. In retrospect, his smoking and occupational history could have contributed risk factors for development of malignancy. However, until autopsy, no laboratory studies revealed carcinoma in either lung or kidney. His initial presentation suggested a possible psychogenic component with grief over his brother's death. However, his persistent disorientation and the extreme hypotension and hypothermia despite the passage of time, treatment for infections, and changes in medication, indicated an atypical syndrome of uncertain medical etiology. His autonomic signs and his delirium on and off psychotropic medications pointed to an etiology other than a degenerative dementia or iatrogenic delirium. Patients with limbic encephalitis can exhibit a prominent impairment of recent memory in combination with behaviors that range from depression and paranoia in a relatively intact sensorium to agitation and atypical bizarre actions with confusion and disorientation.

This case emphasizes the need to take the full medical and psychiatric presentation into account in patients with atypical syndromes. Paradoxical or unusual responses to psychotropic medications or inexplicable autonomic and neurological findings should encourage exhaustive investigation for occult medical disorders. In cases of limbic encephalitis, serial mental status and neurological examinations, EEGs, and lumbar punc-

tures would be most helpful in determining the progressive emergence of the specific etiology.

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