

Brain Involvement in Hodgkin's Disease after 15 years passed of remission: Report of a Case

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Abstract

The case of a 52 old women with Hodgkin's disease of 15 years duration is described. During 4 months ago when she be in the remission phase during every 6 months her follow up she complaint with paranoid minds, urinary incontinency, headache, dizziness and blurred vision started. Papilledema and left hemiparesia were detected. Brain MRI pointed to intracranial invasion by the disease. Therapeutic test with steroids brought to amelioration; therefore, subsequent skull irradiation and chemotherapy were given which improved her condition markedly. For the diagnosis we need newer diagnostic procedures that enable for correct diagnosis of intracranial involvement in Hodgkin's disease. In doubtful cases, therapeutic test with steroids, followed by chemotherapy and skull irradiation, are indicated, and surgery should be advised only if these measures fail.

Keywords: Hodgkin's disease, Psychosis, Brain involvement, Papilledema, Hemiparesia, Steroid treatment

Introduction

In 1960, Brierley et al.(1) described three patients with subacute progressive encephalitis affecting mainly the "limbic lobes", in which inclusion bodies could not be identified. One of these patients was confirmed by autopsy to have bronchial cancer, but no evidence of cancer was found in the other two patients. In 1968, Corsellis et al.(2) described three more cases of patients with bronchial cancer and "limbic encephalitis" and proposed a connection between cancer and limbic encephalitis. These early reports associated the clinical symptoms of memory and mood disturbances with the neuropathological changes of inflammation and degeneration concentrated in the limbic grey matter. These symptoms were not caused by direct neoplastic invasion, thus defining the syndrome as a paraneoplastic condition.(3) Although most cases of paraneoplastic limbic encephalitis have been associated with small cell carcinoma of the lung, associations with cancers of the breast, stomach, colon, kidney, bladder, ovary, uterus, and testicle

have also been reported.(4- 7) In addition, four previous cases of paraneoplastic limbic encephalitis associated with Hodgkin's disease (also known as Hodgkin's lymphoma) have been described.(8-11) We describe a patient who developed prominent memory, behavioral, and mood disturbances which in turn, was found to be caused by Hodgkin's lymphoma.

Case Report

A 52-year-old woman was transferred from her family regarding subacute mental status changes. Six months she transfers, by her family that noticed a subtle urinary incontinency to a psychologist. She treated with antipsychotic drugs after a normal brain CT scan with diagnosis of personality change, without good response and after spent of 4 months that hemiparesis event occure, brain MRI recommended. Two months before the transfer, she showed personality changes, including depressed mood, paranoia. She was intermittently confused and incoherent. Although no one observed any loss

of consciousness, she suffers from hemiparesis recently.

Her past psychiatric history revealed an adjustment disorder with depressed mood in her 20s. Her medical history included a remote head injury requiring stitches. She was otherwise healthy and was taking no prescription medications, but she had been taking homeopathic and herbal supplements. She did not use cigarettes, alcohol, or illicit drugs. She had no family history of psychiatric illnesses, but her father had a history of prostate cancer and a paternal aunt had a history of breast cancer.

Her symptoms led to a 2-day psychiatric hospitalization for depression, and treatment with paroxetine and clonazepam was begun. Shortly after discharge, she became lost while driving to and from work, returned to her home after midnight, and crashed her car into the garage. She was then rehospitalized for further evaluation.

During this second psychiatric hospitalization, she had fluctuating sensorium and hypersomnolence, leading to a brief stay in the neurologic intensive care unit. She also had visual hallucinations. At times she was paranoid and aggressive, striking a nurse and another patient. She required multiple instances of seclusion and physical restraint. Haloperidol, fluphenazine, risperidone, ziprasidone, and quetiapine were tried without sustained improvement of her psychiatric symptoms. The results of a physical examination, laboratory tests, a magnetic resonance imaging (MRI) scan and a computerized tomography (CT) scan of the head, and lumbar puncture were remarkable for a higher than normal creatine kinase level of 2396 U/liter (thought to be related to her struggling when restrained) and a higher than normal nucleated cell count of 30 found by means of the lumbar puncture. Results of a second lumbar puncture were normal. After almost 4 weeks of hospitalization, no medical etiology was found, and electroconvulsive therapy for behavioral control was recommended. Her family then requested a transfer to our institution.

On admission, a mental status examination revealed a tall, thin, slightly disheveled, and bewildered middle-aged woman who was calm, cooperative, and polite. Her speech was soft and slow. Her mood was dysphoric with restricted affect. Her thought process was disorganized, and she fluctuated in her ability to track conversations. She was not overtly paranoid and had no perceptual disturbances. She was alert but not oriented to place or time. Her memory was poor, and she acknowledged that her mind was "a little fuzzy." She was surprised to learn

that she had assaulted others while at the previous hospital. Her score on the Mini-Mental State Examination was 20/30. She denied suicidality or homicidality. The results of a physical examination were initially unremarkable.

We embarked on an extensive medical and neurologic evaluation. A CBC showed a mild anemia (hemoglobin level of 11.7 g/dl) and a normal leukocyte count. Tests of electrolyte levels showed higher than normal bicarbonate (32 mEq/liter) and creatinine (1.2 mg/dl) levels. The magnesium level was high (2.2 mg/dl), and the calcium level was normal. Results for tests of sedimentation rate, liver function, and levels of ammonia, creatine kinase, angiotensin-converting enzyme, sensitive thyroid-stimulating hormone, thyroperoxidase antibodies, anti-double-stranded DNA antibodies, rheumatoid factor, and antinuclear antibodies were normal. The result of a test for cytoplasmic pattern antineutrophil cytoplasmic antibodies was negative, and the result of a test for perinuclear antineutrophil cytoplasmic antibodies was mildly positive. Hepatitis and HIV serologies and tuberculosis skin testing were conducted. The results were negative. Subsequent testing showed a low albumin level (3.0 g/dl) and a high lactate dehydrogenase level (290 U/liter).

The results of serum paraneoplastic studies, including screening for acetylcholinesterase binding antibodies, type 1 anti-neuronal-nuclear antibody, type 2 anti-neuronal-nuclear antibody, type 1 anti-Purkinje-cell antibody, amphiphysin antibodies, striated muscle antibodies, and N-type and P/Q-type calcium channel antibodies, were negative.

Urinalysis suggested a urinary tract infection for which she was treated with a 7-day course of ciprofloxacin. The result of a second urinalysis after treatment was within normal limits. The results of urine heavy metal and porphyria screening tests were normal.

CSF analysis showed six nucleated cells per milliliter (95% lymphocytes, 5% monocytes) and normal glucose (55 mg/dl) and protein (37 mg/dl) levels. CSF cultures showed no microbial growth. CSF polymerase chain reaction tests for Lyme disease, herpes simplex virus, *Toxoplasma gondii*, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, JC virus, and Whipple's disease were negative. The result of CSF 14-3-3 protein testing to rule out Creutzfeldt-Jakob disease was within normal limits. CSF VDRL and cryptococcus antigen testing were also negative.

An MRI scan of the head with and without contrast, including axial FLAIR (fluid-attenuated inversion recovery pulse sequence) and diffusion-weighted imaging, revealed only fluid in the left maxillary sinus. An EEG showed mild diffuse nonspecific background slowing.

She continued to have waxing and waning consciousness. Lucid moments alternated with hypersomnolence, disorientation, paranoia, and visual hallucinations of children or papers by her bedside. Because she was frequently agitated, she was often in seclusion and restraints. Treatment with haloperidol, olanzapine, quetiapine, and chlorpromazine did not significantly improve her delirium.

Approximately 1.5 weeks after admission, a CT chest scan obtained to rule out a thymoma revealed enlarged lymph nodes in the mediastinum and adjacent to the left common carotid and subclavian arteries. A physical examination by a consulting internist revealed a palpable left supraclavicular node about 2 cm in diameter. Fine-needle aspiration of this node resulted in identification of an atypical lymphoid population. A subsequent open biopsy revealed the diagnosis of Hodgkin's lymphoma, nodular sclerosing type. A bone marrow biopsy did not show signs of involvement with Hodgkin's lymphoma. CT abdomen and pelvis scans did not reveal adenopathy, and she was given a diagnosis of stage II-A Hodgkin's lymphoma.

It is interesting to note that her agitation resolved 4 days after the fine-needle aspiration and 1 day before the excisional biopsy. The day before the excisional biopsy, she was taken out of seclusion, and her mental status began clearing. She did not remember the events of her hospitalization, but she acknowledged that she seemed to have lost a few days of time. She received her first course of chemotherapy with adriamycin, bleomycin, vinblastine, and dacarbazine later that week and tolerated it well. She was alert, oriented, and had no hallucinations. Shortly thereafter, she was discharged with a treatment plan for outpatient chemotherapy. At discharge, her only psychotropic medication was 5 mg of olanzapine every evening.

At follow-up 3 months later, she was still undergoing a course of chemotherapy. Olanzapine had been discontinued 2 weeks after her hospital discharge, and she experienced no further psychiatric symptoms.

Discussion

The clinical presentations of paraneoplastic limbic encephalitis have been described in numerous

reports and reviews.(1, 2, 5, 7, 12- 15) Limbic encephalitis is marked by the triad of memory impairment and dementia, psychiatric disturbances, and seizures.(15) However, seizure is not an absolute requirement. Onset is usually between ages 50 and 70 years and may frequently be dramatic, with prominent changes in the baseline mental status, including the core features of memory and mood disturbances.(5) There may be elements of depression, anxiety, personality changes, agitation, confusion, hallucinations, perceptual disturbances, paranoia, and bizarre behavior. Patients may initially be hospitalized psychiatrically before an underlying medical etiology is uncovered. Neurologic evaluation may be unrevealing, with normal results for MRI and CT head imaging, nonspecific EEG abnormalities, and, sometimes, lumbar puncture results showing a higher than normal level of protein and mononuclear pleocytosis. Pathological changes are found mainly in the limbic structures, especially in the hippocampus and the amygdala. These changes include neuronal loss with reactive gliosis, microglial proliferation, and perivascular lymphocytic cuffing.(7, 12, 13)

For the patient described in this case report, the clinical presentation was of delirium. Her subacute memory difficulties, followed by personality, mood, and behavioral changes, were consistent with the features of limbic encephalitis. She did not manifest seizures, however. Neuroimaging results were normal, and an EEG showed nonspecific background slowing. CSF studies initially showed a high cell count, but the results of repeated studies were normal. We did not obtain brain biopsy to confirm pathology.

It is noteworthy that the results of serum paraneoplastic studies, which included testing for type 1 anti-neuronal-nuclear antibody (anti-Hu),(16) type 2 anti-neuronal-nuclear antibody (anti-Ri), and type 1 anti-Purkinje-cell antibody (anti-Yo), were negative. The anti-Hu antibody has been found in 20% of 71 patients with paraneoplastic encephalomyelitis and/or sensory neuronopathy who experienced symptoms of limbic encephalitis.(17) Paraneoplastic cerebellar degeneration, another known complication of lung cancer, ovarian cancer, and Hodgkin's lymphoma, has also been associated with the presence of anti-Hu, anti-Yo, and anti-Ri antibodies.(18, 19) Others,(19, 20) have suggested that the anti-Tr antibody is specifically associated with paraneoplastic cerebellar degeneration in Hodgkin's lymphoma. We did not test our patient for the anti-

Tr antibody because she had no cerebellar dysfunction.

Included in the differential diagnosis of limbic encephalitis are the effects of medications and infections. The patient in this case had been taking homeopathic and herbal supplements, one of which contained belladonna and another ephedra, but these substances were thought to be in small amounts, and she had stopped taking the supplements 1 month before her admission to our institution. Hence, we could not attribute all of her symptoms to these supplements. In addition, even though the patient had a urinary tract infection, which could have possibly contributed to her psychiatric symptoms, its adequate treatment failed to resolve her symptoms. We found no evidence for a neurologic infectious etiology.

Four days after she underwent fine-needle aspiration of an affected lymph node, and 1 day before surgical excision of this node, her mental status began clearing. The timing of her improvement remained unclear. Mental status changes associated with Hodgkin's lymphoma have improved with treatment of the lymphoma,(8, 9, 11) but, in this case, the patient had not yet started treatment. Perhaps the fine-needle aspiration reduced the paraneoplastic process affecting her limbic system, and 4 days later she began improving. At discharge, she was without psychiatric symptoms.

The prognosis of paraneoplastic limbic encephalitis is generally poor. Survival time ranges from 1 to 22 months.(5) Henson and Ulrich(12) suggested that the related cancer is more often the direct cause of death; however, Kaniecki and Morris(15) proposed that relentless neurologic deterioration leads to death. Although paraneoplastic limbic encephalitis responds poorly to antineoplastic or immunosuppressive therapy, reversibility in small cell lung cancer has been reported.(15) The prognosis of Hodgkin's-related paraneoplastic limbic encephalitis appears to be good, as three of the four previously reported cases demonstrated reversibility.(8, 9, 11)

Carr,(8) first described limbic encephalitis associated with Hodgkin's lymphoma in 1982 in the case of his teenage daughter, who presented with memory difficulties, personality changes, and psychosis, and who was subsequently discovered to have Hodgkin's lymphoma. In 1990, Pfliegler et al.(9) reported the case of a 33-year-old farmer with Hodgkin's lymphoma who developed behavior changes a few weeks after receiving the diagnosis. Both of these patients eventually recovered from

their neuropsychiatric symptoms after completing lymphoma treatment. In 1989, Maggioni et al.(10) reported the case of a 67-year-old woman with peripheral and central nervous system changes, including memory and behavioral disturbances, who deteriorated and died of a pulmonary embolism within 6 months. The results of an autopsy showed that she had Hodgkin's lymphoma. In 1996, Deodhare et al.(11) provided the first biopsy-proven case of paraneoplastic limbic encephalitis associated with Hodgkin's lymphoma in a 23-year-old male patient who presented with progressive mental status changes and a seizure, and was subsequently given a diagnosis of Hodgkin's lymphoma. This patient also improved after chemotherapy.

In three of these four cases, the clinical presentation of limbic encephalitis preceded the diagnosis of Hodgkin's disease. Seizures were reported in only one case. The patients in three of the four cases improved after chemotherapy. Only the last case included biopsy-proven results to support the pathologic diagnosis of limbic encephalitis.

For the patient described in our case report, the clinical presentation was consistent with limbic encephalitis, which was followed by a diagnosis of Hodgkin's lymphoma and by recovery after biopsy and chemotherapy. In evaluating patients in middle age and later life who display delirium, psychosis, memory disturbances, and mood changes, the clinician should consider paraneoplastic limbic encephalitis as a possible cause of the psychiatric symptoms.

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