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Receptive Aphasia as the Initial Sign of Leptomeningeal Myelomatosis

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Abstract

Multiple myeloma rarely invades the cerebrospinal fluid (CSF). The process is known as leptomeningeal metastases/myelomatosis (LM). Focal symptoms are typical at onset, often with associated pain or delirium. Here we present a patient whose initial relapse began with difficulty understanding language. There was a delay of approximately one month in diagnosis, during which time he became weaker and more confused.

This case highlights the importance of considering LM, even when the disease is thought to be in remission. Despite our patient's poor outcome, prompt initiation of treatment may significantly improve quality of life and prolong survival.

Keywords

Receptive aphasia; Multiple myeloma; Leptomeningeal myelomatosis

Introduction

Multiple myeloma (MM) rarely invades the central nervous system (CNS).When it does so, it is typically late in the disease course; involvement at presentation is exceptional. The most commonly recognized presentations are of weakness, confusion and epilepsy [1]. We present an unusual case in which the patient's initial symptom was gradual-onset receptive aphasia.

Case Presentation

Our patient was a right-handed, retired Caucasian man who had been healthy until age 57, when hairy-cell leukemia was diagnosed on a routine blood test. Cladribine was given as a single cycle and lead to complete remission.

At age 65 he developed back pain. Following blood tests, a bone marrow biopsy confirming the diagnosis of IgG, kappa-chain multiple myeloma (the most common type). He underwent induction chemotherapy with cyclophosphamide, bortezomib and dexamethasone. Additionally, he was treated with radiotherapy, followed by an autologous stem cell transplant (ASCT). He remained on lenalidomide to prevent relapse.

His clinical course is shown in Table 1, with day zero corresponding to the time when transferred to our institution. He initially presented to an outside facility with a three-week history of receptive aphasia, ideational apraxia, headaches and episodic confusion. Thereafter, he presented to the emergency

room on five occasions and was admitted on four. His headache worsened and he developed signs of elevated intracranial pressure, including increasing lethargy, worsening memory and occasional vomiting. His legs became weak, leading to difficulty with ambulation. He had intermittent visual hallucinations. Magnetic resonance images (MRI) of the brain were reported as unremarkable on two occasions, including one with contrast. Lumbar puncture (LP) showed elevated opening pressure, protein, and nucleated cells present; however cytology did not reveal the diagnosis.

Following transfer, an MRI showed diffuse leptomeningeal enhancement, including the spinal cord. His MRI's are shown in Figures 1-3. Repeat LP showed an increase in opening pressure, persistent lymphocytosis and increased protein. Cytology confirmed plasma cells in the CSF. Elevated immunoglobulins were also present, particularly IgG, which was almost 2000 times the upper limit of normal. Serum protein electrophoresis (SPE) confirmed an IgG M-spike.

A ventriculoperitoneal shunt (for hydrocephalus) and an Ommaya reservoir (for intrathecal chemotherapy) were placed. Dexamethasone was started and he received whole brain radiation as well as focal radiation to the thoracic spine. One dose of intrathecal liposomal cytarabine was given.

Despite these measures, he declined rapidly. He developed increasingly frequent staring spells and was treated for epilepsy. Dysphagia supervened, leading to aspiration pneumonia. The patient died shortly thereafter in hospice, approximately eight weeks after his initial presentation.

Discussion

MM is a cancerous proliferation of immunoglobulin-producing plasma cells. It accounts for approximately one percent of all cancers and approximately ten percent of hematologic malignancies in the United States, with an incidence of 1/100,000 [2]. When suspected, confirmation is sought with tests such as a complete blood count, SPE and a 24-hour urine collection for electrophoresis and immunofixation, followed by bone marrow aspiration and biopsy. The diagnosis requires the presence of a monoclonal (M) protein in serum and/or urine, a high proportion of bone marrow clonal plasma cells (≥10%) and the presence of related organ impairment due to plasma cell infiltration (e.g. anemia, renal insufficiency, hypercalcemia, lytic bone lesions). The most neurologic symptom is radiculopathy of the thoracic or lumbosacral area, due to compression or collapse of bone.

Virtually all patients who receive ASCT for MM relapse, typically within 10 years, often within one year. Hence the rationale for long-term adjuvant chemotherapy, particularly in those considered intermediate or high-risk based on cytogenetic studies. Lenalidomide and thalidomide are first line agents for this purpose, although thalidomide has a higher rate of peripheral neuropathy. Penetration to CSF is estimated at 11% and 42% respectively, which is comparable to agents used systemically for treatment of LM, such as cytarabine, methotrexate and corticosteroids [3]. LM has been reported in spite of treatment with these agents (as well as adjuvant bortezomib). It remains unclear if these agents play a role in prophylaxis of LM.

Surveillance is usually done by monitoring M-protein in serum and urine. In some cases, serum light chain assay or bone marrow biopsy are required. While not recommended routinely, PET/CT scan is helpful in determining prognosis following initial treatment. It is also used at the time of diagnosis to supplement the standard skeletal survey. Whole-body MRI has likewise been employed for this purpose.

LM is thought to occur in one percent of cases of MM. Patterns of relapse of MM have best been described by Zamarin et al. who report 273 cases. Just one relapsed as LM, and this was one of six (2%) relapsing patients without serologic evidence [4]. Symptoms at onset of LM in MM have been reported in 23 patients. The majority already had progressive disease – only one was present at initial diagnosis. Seven had confusion at onset and *none* were recorded as having antecedent cognitive decline. The time to developing LM had a median of 13 months (maximum 29 months) [5]. Another series of 17 patients had a median time to LM of 36 months (maximum of 9.5 years) [6]. These durations are longer than is usual with systemic relapse, suggesting a dormant pool of cells within the CNS. It has been suggested that the likelihood of CSF relapse increases over time, with cases reported up to 10 years following initial treatment, although reports are too scarce to draw firm conclusions [7]. Certain subtypes of MM appear to have a propensity to develop LM: a study of nine such patients identified p53 deletions in eight and deletions of chromosome 13q in four [8]. This 13q deletion is a poor prognostic factor, commonly involves the RB-1 (retinoblastoma) region and is rarely though to be rare in the euploid forms of MM [9].

LM can be diagnosed clinically, although confirmatory evidence from CSF is almost always sought. MRI should normally be undertaken first, in order to avoid distortion of images due to persistent CSF leak following lumbar puncture. Typical findings on MRI include leptomeningeal enhancement with contrast and FLAIR hyperintensity within the subarachnoid space (due to the high protein content). In the series above, CSF was abnormal in all patients, usually exhibiting pleocytosis, elevated protein, and positive cytology for plasma cells [17]. Falsely negative cytology appears exceptionally rare. Flow cytometry is a useful adjunct in diagnosis [10]. Measurement of CSF immunoglobulin can also provide confirmatory evidence.

The long preceding history of cognitive decline is remarkable. His problems with language may be attributed to dysfunction of the dominant temporal lobe. Lenalidomide appears unlikely as a contributor to his cognitive symptoms, especially as stopping this seemed to confer no improvement. Confusion is listed as affecting less than one percent of users and most likely would be expected earlier in the disease course [1].

His subjective symptom of dragging the left leg when walking on his second emergency presentation is suspicious for involvement of the brain or lumbar nerve roots at this time. While his neurological exam was repeatedly documented as being normal, it is not clear that leg strength was stressed e.g. standing, hopping or walking while squatting.

Elevated CSF pressure causing hydrocephalus is common with LM and is due to impaired drainage as a result of blockage. Our patients worsening headaches followed by difficulty walking without clear weakness on exam are typical. As this is likely to be rapidly reversible, a ventriculoperitoneal shunt is recommended, which can be placed simultaneously with an Ommaya reservoir if intrathecal treatment is to be pursued.

As LM typically occurs late in the disease course, it often has a grave prognosis. Intrathecal chemotherapy showed an improvement in median survival from two to 20 months in one series of 17 patients [15]. Methotrexate, cytarabine and dexamethasone were all employed for this purpose, sometimes together. Although radiation was not associated with survival in these patients, its use appears rational based on the tumors known radiosensitivity and encouraging results with other tumors

with leptomeningeal spread. The only two survivors at the time of writing of the above series had received both treatments, in addition to systemic bortezomib.

Regarding systemic chemotherapy, changing lenalidomide to thalidomide would appear to be a reasonable choice in light of its pharmacokinetics. An alternative is the addition of clarithromycin to lenalidomide, which is well tolerated and was noted to lead to at least partial response in 40% of 24 patients in a recent series (although none had involvement of the CSF) [11]. This works in part by CYP450 inhibition and in part by its immune-modulatory properties. Most patients are likely to be too unwell to tolerate repetition of transplant, although a second ASCT has been reported to result in remission in one case, where it was used following cranio-spinal irradiation [12]. Prophylaxis for the expected graft-versus-host disease was not undertaken, as is usual; this was thought to have contributed to the patient's recovery. He remained well 9 months the procedure.

Conclusion

We hope that this case will underscore the importance of considering MM (and leukemia/lymphoma in general) as a cause of receptive aphasia, cognitive impairment or dementia. This should be a particular concern in patients with a prior history of disease, even when this is thought to be in remission. As treatment of disease elsewhere in the body improves, this problem is likely to become ever more prevalent. Prompt initiation of treatment can lead to improved outcomes for patients with this complication.

Figures

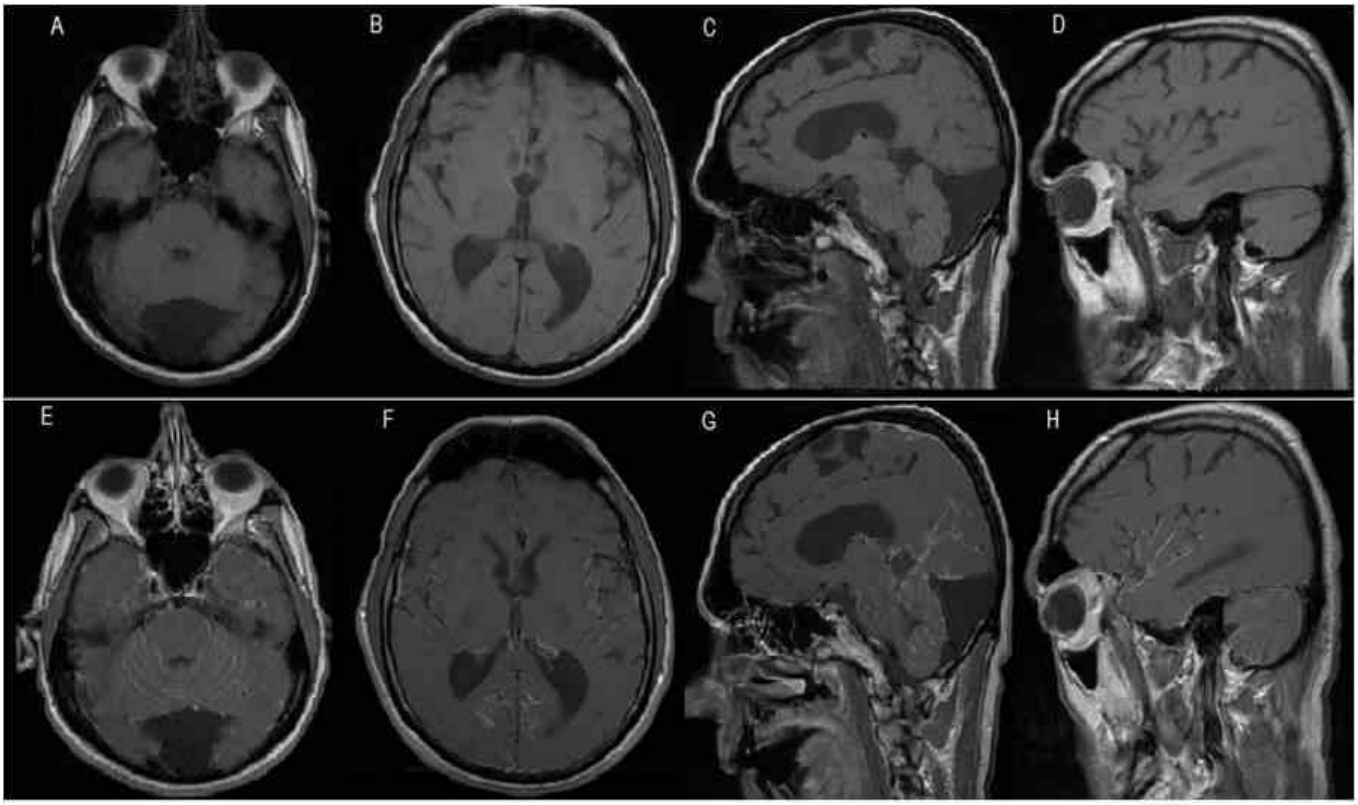

Figure 1: MRI Brain with and without contrast, on day 0. A-B – Axial T1 pre-contrast. C-D – Sagittal T1 pre-contrast. E-F – Axial T1 post-contrast. G-H – Sagittal T1 post-contrast.
A-D. T1 pre-contrast imaging reveals no leptomeningeal enhancement.
E-H. Diffuse leptomeningeal enhancement post-contrast is seen. Incidental mega cisterna magna noted.

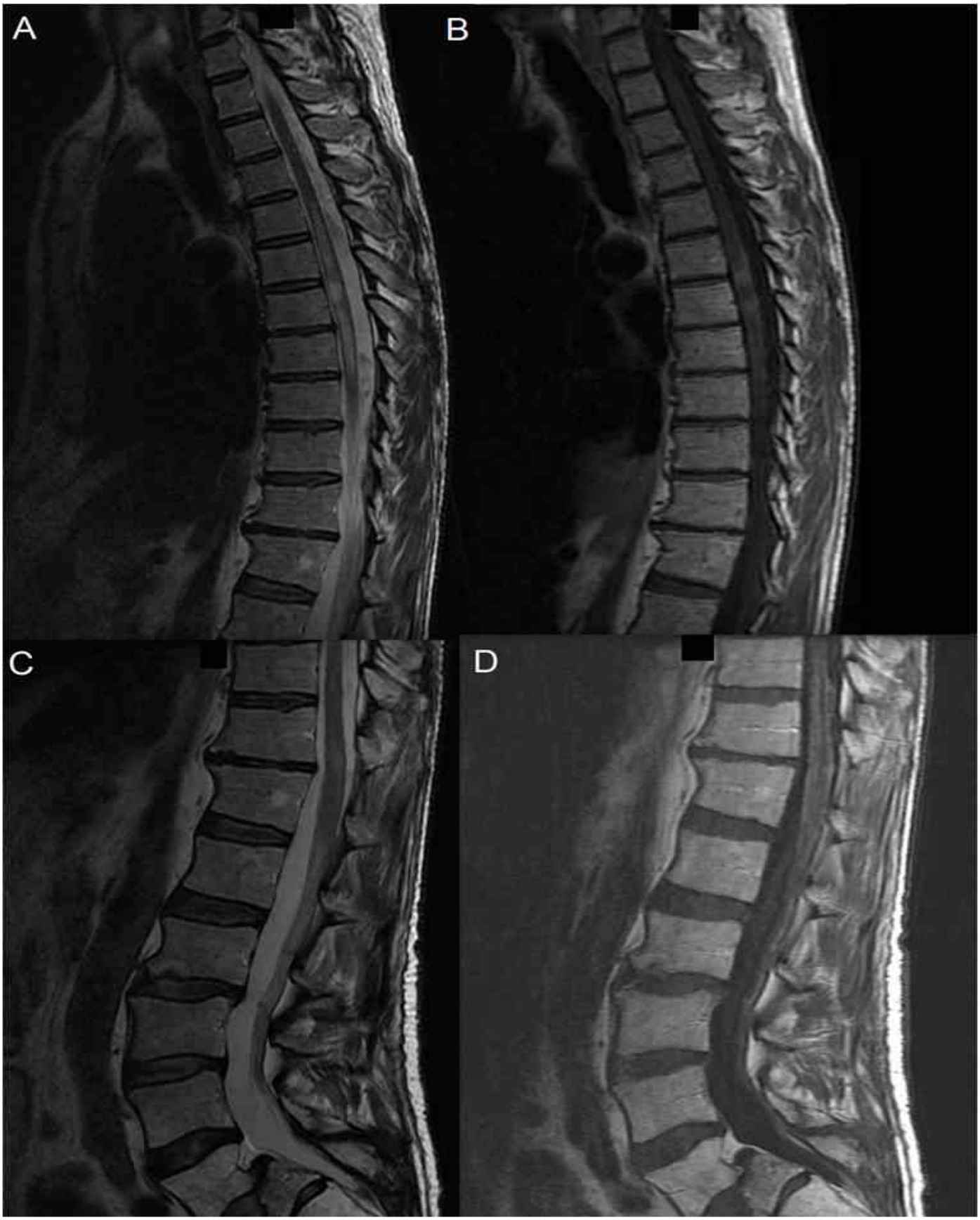

Figure 2: MRIs of spinal cord, day 3. A, C – T2 weighted (fast spin-echo). B, D – T1 post-contrast.
A-B. There is intramedullary enhancement at T9 vertebral level with extensive T2 hyperintensity which extends longitudinally along at least four vertebral levels.
C-D. Dural (leptomeningeal) enhancement is visible along the distal spinal cord, conus medullaris and cauda equina.

Table

Time	Symptoms/ signs	Investigations	Working diagnosis
- 1 year	"Difficulty understanding certain expressions".		
- 3 months		Small serum M-spike noted; Unable to characterize further. PET/CT of body normal.	
- 2 months	"At times he would get his words mixed up".		
- 35 days ER	3 days prior: trying to answer coffee cup as if it was his phone. Lasted < 1h, sleepy thereafter. Headache, abnormal speech.	MRI brain +contrast - N Carotid u/s - N Echo- N	Possible TIA vs. "transient confusion"
- 19 days ER	"I couldn't hear audible noises" lasting 1h. Recurrent language problems lasting 1h, sleepy afterwards. Emotional lability. Short term memory loss. Receptive aphasia. Circumlocution; paraphasic errors. Could follow visual cues. Dragging left leg when walking.	EEG (30 mins) - N (drowsy with appropriate changes) MRI brain +contrast - N MRA head and neck - N	Lenalinomide-induced
- 7 days ER	Fall. Head and neck pain radiating to shoulders. Memory deteriorating.		Probable dementia
- 5 days ER	Falls due to leg weakness.		
- 3 days ER	Unable to walk x10 days; sleeping on sofa. 1 day confusion w/headache. Withdrawn; flat affect. Combative during CXR. Initial exam recorded as N. "Sensorium improved transiently after LP".	MRI not possible x3 as agitated. CSF: OP 33, CP 16, 9ml sent. WBC 63 (lymphocytic), protein 127, glucose 57. Cytology (0.5ml): dis-cohesive cells with small, dark nuclei.	Viral encephalitis vs. paraneoplastic
Care transferred			
0	No insight. Cannot recall wife's name or do arithmetic. Disoriented. Hallucinatory. Power 3/5 strength throughout.	Monoclonal spike IgG kappa present. Kappa/lambda light-ratio 1.75 (<1.65). MRI brain – leptomeningeal enhancement. CSF: OP > 55cm H20. RBC 1, WBC 29 (80% lymphocytes), protein 170, glucose 65. IgM 30 mg/dLt (<0.02), IgG 770 (<0.4), IgA 105 (<0.03). Cytology +ve myeloma.	LM

Day 1	WBRTx started; 3Gy x10 fractions.	MRI spine – leptomeningeal enhancement.	
Day 4	Ventriculoperitoneal shunt + Ommaya placed.	EEG(30 mins) - diffuse slowing, FIRDA. CSF (from Ommaya): RBC 2, WBC 7 (94% lymphocytes), protein 42, glucose 80.	
Day 8	IMRTx T5-8 started; 3Gy x5 fractions.		
Day 9	Liposomal cytarabine 50mg via Ommaya.		
Day 14	Transferred to Hospice.		
Day 21	Died		

Abbreviations:
ER - emergency room visit
N – normal
M-spike – monoclonal
PET/CT – positron emission tomography/ computer tomography
MRI – magnetic resonance imaging; MRA - magnetic resonance angiography
u/s – ultrasound
echo - echocardiogram
CSF – cerebrospinal fluid; OP – opening pressure (cm water); RBC – red blood cells; WBC – white blood cells
EEG – electroencephalography; FIRDA – frontal, intermittent rhythmic delta activity
WBRTx – whole brain radiation therapy; IMRTx – intensity-modulated radiation therapy; Gy - Gray

Table 1. Clinical course. Blood tests normal (repeatedly, if tested more than once): CBC, CMP, TSH, CRP, B12, MMA, folate, ammonia, HIV. CSF –ve for HSV (via PCR).

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