Brain Amyloidoma With Cerebral Hemorrhage

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Unlike systemic amyloidosis, the diagnosis of brain amyloidoma without systemic manifestations is clinically challenging. Despite the availability of advanced brain imaging technology, such conditions are difficult to ascertain without brain biopsy or autopsy. We report the case of a 64-year-old woman who presented with frontal lobe syndrome with abnormal linear enhancement on brain magnetic resonance imaging. Results from a stereotactic biopsy revealed $\alpha$-positive protein deposition in the brain parenchyma. During the course of illness, the patient had an acute cerebral hemorrhage, which manifested with hemiparesis, dysarthria, and pathologic crying. Review of the literature revealed 15 cases of primary brain amyloidoma. Patients had similar protein deposits but in different regions of the brain and therefore presented with various neurologic symptoms.


Systemic amyloidosis is usually caused by plasma cell dyscrasias, chronic inflammation, or hereditary disorders. A localized or tissue-specific mass of amyloid protein accumulation is called primary amyloidoma and has been described in the soft tissues of various organs, with a predilection for the kidneys, liver, and heart. In the brain, amyloid deposition can be limited to the cerebral vessels, as in cerebral amyloid angiopathy, or in the extracellular matrix of the white matter of the brain parenchyma, as in brain amyloidoma. Only 15 cases of amyloidoma in the brain parenchyma have been reported in the literature. The condition’s indolent course may contribute to this limited number of reports.

We present a rare case of amyloid deposits in the brain that manifested initially with frontal lobe syndrome and later with a cerebral hemorrhage. These manifestations were associated with plasma cell dyscrasias and monoclonal gammopathies. To compare our clinical experience to previous reports, we also review the literature for similar cases.

Report of Case

In September 2006, a previously healthy 64-year-old woman presented to University Hospitals Case Medical Center in Cleveland, Ohio, with complaint of difficulty concentrating, memory loss, behavioral changes, and pervasive fatigue. She reported that these symptoms had occurred for 1 month. She also described having a poor appetite and losing 9 lb unintentionally in the 3 weeks before presentation. The patient’s family confirmed her changes in personality—from being active and outgoing to preferring daytime naps and avoiding social interaction with friends and relatives. She battled intermittent depression throughout her adult life without the use of pharmacologic treatment.

Physical examination revealed an alert and oriented woman without distress. She was afebrile and had a blood pressure level of 130/78 mm Hg; heart rate, 70 beats per minute; and respiratory rate, 16 breaths per minute. The initial general and neurologic examinations were normal except for subtle signs of frontal lobe dysfunction, which included apathy and blunted affect. Language and cranial nerve function were normal. In addition, the patient had no signs of upper or lower motor neuron dysfunction.

The patient was initially treated with an antidepressive agent, but this therapy failed to reverse her symptoms within 6 months, prompting further investigation. Magnetic resonance imaging (MRI) scans of the brain with linear enhancement revealed multiple lesions in the subcortical white matter of the right frontal and left parietooccipital lobes (Figure 1). Results from a diffusion-weighted MRI were normal. Electroencephalography results showed a normal background rhythm without periodic patterns.

We suspected infectious, inflammatory, and infiltrative processes and therefore ordered a battery of tests. Findings included a normal sedimentation rate as well as normal levels of C-reactive protein, anti-nuclear antibody, and angiotensin-converting enzyme. She also had normal serology for human immunodeficiency virus, syphilis, and Lyme disease. Serum...
immunoelectrophoresis showed an elevated M-protein level (0.3 g/L), which was characterized as monoclonal k-protein. Analysis of cerebrospinal fluid revealed a normal total serum protein level (45 mg/dL) without pleocytosis (1 nucleated cell/mm³). Protein electrophoresis of the cerebrospinal fluid showed a positive oligoclonal band with normal immunoglobulin-albumin ratio and index and normal immunoglobulin synthesis rate. Urine immunoelectrophoresis revealed no spillage of the monoclonal protein.

Because the results of a cerebral angiography were normal, the patient underwent a left frontal lobe stereotactic biopsy approximately 8 months after initial presentation. Pathology specimen was examined and found to have extensive vascular and extracellular amyloid protein deposition in the white matter consistent with the clinical diagnosis of diffuse brain amyloidoma (Figure 2). Furthermore, immunohistochemistry results showed k-negative, λ-positive protein type (Figure 3). A bone marrow biopsy demonstrated 5% λ-positive plasma cell dyscrasias without evidence of plasmacytoma on bone or soft tissue. Chemotherapy and immunosuppressive therapy were recommended, but the patient refused treatment.

Three months later, the patient suffered a right frontal lobe cerebral hemorrhage that manifested with severe headache, dysarthria, and left-sided hemiparesis (Figure 4). She also developed severe emotional lability with pathologic crying but without laughter. Prothrombin and activated partial thromboplastin times, liver enzymes, and platelet count were normal. The patient consented to immunosuppressive therapy with a high dose pulse dexamethasone (40 mg daily for 4 days biweekly) and thalidomide (200 mg/day). Despite therapy, a repeated MRI of the brain showed an increasing confluence of lesions in the white matter in both cerebral hemispheres consistent with progressive disease. For emotional lability, she was treated with sodium valproate (500 mg per day).

Six months after initiation of dexamethasone therapy, the patient developed severe dexamethasone-induced myopathy, and the steroid treatment was replaced with oral melphalan (6 mg/day). Motor strength improved, emotional lability and fatigue subsided, and memory deterioration stabilized. Two years later, she remained in good health with undetectable monoclonal M proteins on serum immunoelectrophoresis with immunosuppressive therapy. Valproate therapy was stopped 6 months later, but the patient continued melphalan therapy.

Discussion

Amyloidoma of the brain parenchyma is a rare form of non-systemic amyloidosis. Although the clinical presentation reported in previous cases varied, epilepsy and dementia were most frequently cited. Other reported symptoms included depression, headache, and visual loss or field defect.

Three months after initial presentation, the patient described in the present report exhibited pathologic crying, which has been reported with neurologic conditions such as traumatic brain injury, ischemic stroke, and multiple sclerosis. Although the exact mechanism of pathologic crying is not well understood, it is likely related to a dysfunction in
prefrontal regulation of the limbic circuits, resulting in troubled emotional expression.17

Of the 15 cases of brain amyloidoma, lethal hemorrhage occurred in one patient.12 Unlike cerebral amyloid angiopathy, in which the risk of intracranial hemorrhage is known to be high,20 the risk of hemorrhage in brain amyloidoma is undetermined. However, because amyloid deposition in brain amyloidoma occurs in the brain parenchyma as well as in the cerebral vessels, the risk of hemorrhage may be equal. The risk of bleeding in systemic amyloidosis is further increased as a result of concurrent coagulopathy.21

Imaging studies varied among the reported cases of brain amyloidoma. A computed tomography (CT) scan of the brain may show hypo- or hyperdense signals in the subcortical white matter, as described in one case report.3 An MRI scan of the brain revealed hypointense lesions on T1-weighted images—with or without contrast enhancement—in the majority of the reported cases.3,11-16 Also, a T2-weighted MRA showed predominantly hyperintense or mixed intensity signals in some reports,3,14,22 perhaps correlating with the variable accumulation of amyloid protein. Linear enhancement with gadolinium administration was present in our patient as well as in a previously reported case by Cohen et al.11

Because of the variable clinical and radiologic features of brain amyloidoma, stereotactic biopsy is needed to confirm the diagnosis and to identify the type of protein deposits.13,23

Figure 2. Histopathology sections from the left frontal lobe of a 64-year-old woman who presented with frontal lobe syndrome. Hematoxylin-eosin (A) and eosin (B) stains showed amorphous eosinophilic amyloid protein deposition in the brain parenchyma and vascular wall. Congo-red stain (C) and polarized light microscopy (D) revealed positive birefringence. These findings were consistent with brain amyloidoma.

Figure 3. Immunohistochemistry stains from a 64-year-old woman with brain amyloidoma. Stain results were negative for κ protein (A) and positive for λ protein (B).
Lambda light-chain protein type was present in the majority of the reported cases.3,4,11,13,15,16

Barring co-existence of systemic manifestation, survival of patients with isolated brain amyloidoma varied from a few years to 17 years, as noted in a 2008 report.22 By contrast, amyloidosis with multiple system involvement is a rapidly progressive disease that could lead to death within a year if untreated.24

Among patients’ treatment options, chemotherapy for plasma cell dyscrasias is proposed to suppress amyloid production. Autologous peripheral blood stem cell transplantation after a cycle of melphalan is the most effective therapy for patients with amyloidosis.25 High-dose oral melphalan with dexamethasone is the preferred alternative medication for patients with systemic AL amyloidosis who are not candidates for stem cell transplantations.26

Conclusion
Brain amyloidosis is a rare syndrome that presents with various neurologic manifestations and increases patient risk of cerebral hemorrhage. Physicians should confirm the clinical diagnosis with a brain biopsy. In rapid disease progression or in the presence of systemic disease, immunosuppressive therapy is warranted.

References