Case Report

Intracranial and systemic manifestations of familial leptomeningeal amyloidosis, as seen on CT and MRI

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Abstract

Leptomeningeal amyloidosis is a subset of familial transthyretin amyloidosis, a family of diseases occurring in conjunction with multiple known mutations of the transthyretin gene. Though this is primarily a disease of the central nervous system, amyloid deposition is multisystemic. We describe a case of a 61-year-old man with known central nervous system amyloidosis presenting to the emergency room with stroke-like symptoms, including left hemineglect, right gaze paresis, and left hemiplegia, atop baseline dementia. A noncontrast CT head demonstrated ventriculomegaly and no acute hemorrhage. Urinalysis indicated an underlying urinary tract infection, ultimately believed to have prompted a breakthrough seizure. Electroencephalogram revealed diffuse encephalopathy. Contrast-enhanced MRI demonstrated hallmarks of intracranial amyloid with no new infarct. Previously taken noncontrast CT neck and thorax demonstrated evidence of systemic disease.

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Background

Amyloidosis is a disease of accumulation, characterized by the extracellular deposition of abnormally folded protein fibrils. It is most commonly multisystemic, with immunoglobulin light chain, chronic inflammatory amyloidosis, and the familial amyloidoses all occurring in multiple organ systems (central nervous system, kidneys, heart, lungs, and gastrointestinal system). Transthyretin-associated amyloidoses (ATTR, occurring in conjunction with abnormal mutation of the TTR gene) cause multisystemic disease, typically with predominance of cardiomyopathy or peripheral neuropathy. Leptomeningeal or oculo-leptomeningeal amyloidosis, however, is a transthyretin

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Fig. 1 – T1-weighted brain MRI without (left) and with (right) contrast demonstrate marked leptomeningeal enhancement (yellow arrows) with involvement of the seventh and eighth cranial nerve complexes, particularly on the right (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Fig. 2 – T1-weighted brain MRI demonstrates marked leptomeningeal enhancement in supratentorial (blue arrows) and infratentorial (yellow arrows) compartments, as well as along the surface of the brainstem (red arrows) and cervical spinal cord (green arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3 – Contrast-enhanced coronal FLAIR image demonstrates diffusely abnormal signal and enhancement throughout the sulci (yellow arrows), particularly within the Sylvian fissures (red arrows), as well as within the basal cisterns (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Case presentation

A 61-year-old man, diagnosed at age 49 in 2004 with leptomeningeal amyloidosis, presented to the emergency room with altered mental status, hemineglect, and gaze paresis. Per his wife, he had been displaying worsening confusion and staring episodes for the past months. Initial noncontrast head

amylodosis with extensive manifestation in the central nervous system. While the disease was initially thought to occur exclusively in European populations, incidence (with the causative mutation, Leu12Pro) has also been documented in patients of African origin [1]. Presentations include dementia, seizure disorders, spasticity, ataxia, and sensorineural hearing loss [2], secondary to amyloid deposition in leptomeningeal vessels. Here, we present a case of a man of European origin with oculoleptomeningeal amyloidosis, whose imaging is
CT showed ventriculomegaly and no hemorrhage. He was admitted to the hospital.

He has presented several times in the past with similar episodes of transient hemiparesis and other neurologic deficits, attributable to seizure. His initial presentation, which ultimately lead to the diagnosis of amyloidosis, consisted of such an episode, where he was admitted having had 3 tonic-clonic seizures. His neurologic exam at that time was significant for altered mental status and right gaze preference, as well as decreased strength on his left side, left-side hyper-reflexia, left hemisensory deficit, and left-sided ataxia.

His past medical history is otherwise pertinent for some degree of length-dependent neuropathy, which is consistent with the more common presentation of transthyretin-associated amyloidosis, associated with deposition in the peripheral nervous system (it is not described within the classic CNS confines of oculoleptomeningeal [3-5]. On prior imaging, the patient had also demonstrated hydrocephalus. He had had therapeutic removal of CSF 1 year prior, which had modestly improved his gait, but failed to treat his dementia (his most recent MOCA score, taken immediately after removal of CSF, was 11). Past medical history is also significant for coronary artery disease, hyperlipidemia, and previous cerebral infarct. The patient has had gait problems for 7 years. He also suffers from bilateral hearing loss, believed to have started 9 years prior, and nocturnal incontinence since 2 years prior.

The patient’s surgical history is significant for the removal of a laryngeal papilloma, 9 years earlier. CT neck and thorax taken at that time showed additional glottic nodularity and widespread interstitial nodularity in the lung, indicative of amyloid deposition. He has a strong familial history of familial oculoleptomeningeal amyloidosis on his father’s side, with a known transthyretin val30gly missense mutation. Genetic
testing confirmed this mutation in both himself and his father.

Upon presentation, physical exam was unremarkable in respiratory, cardiovascular, and abdomen. The patient was oriented to time and place, but had difficulty following commands. Further neurologic exam demonstrated right gaze paresis and diminished hearing bilaterally. Strength was 5/5 on the right, but only antigravity movements were preserved on the left. Sensation was preserved on the right, but absent in the left upper and lower limbs. Reflexes were normal bilaterally. The patient was able to ambulate with a wide gait, using an assistive device.

**Investigations**

The patient’s urinalysis was positive for leukocyte esterase and nitrites and 4+ bacteria.

EEG demonstrated encephalopathy but no seizure activity.

A head CT demonstrated no hemorrhage, but did show communicating hydrocephalus. A brain MRI was ordered with and without contrast, to assess for new areas of infarction. None were appreciated. However, imaging showed marked diffuse leptomeningeal enhancement in both supra and infratentorial compartments.

**Treatment, outcome, and follow-up**

Per his urinalysis, the patient was started on ceftriaxone. By hospital stay day 5, his gaze paresis had resolved and he was following commands.

The patient was diagnosed with a urinary tract infection with contribution to infectious encephalopathy. This is thought to have exacerbated his standing cognitive disease of familial oculoleptomeningeal amyloidosis, ultimately triggering breakthrough seizure and prompting his hospitalization.

The patient was discharged home on day 8, and currently follows with a neurologist.

**Discussion**

Oculoleptomeningeal amyloidosis manifestations occur primarily in the central nervous system, though like all amyloidosis, deposition is systemic [5]. Patients may suffer seizures, recurrent headaches, hearing loss, cognitive decline, and gait...
disturbance, all of which are concurrent with leptomeningeal amyloid deposition. This patient’s known headaches and stroke-like episodes were, prior to his diagnosis of amyloidosis, believed to be hemiplegic migraines. As with any leptomeningeal process, hydrocephalus can be observed in association with impairment of CSF reabsorption. Given that this patient’s clinical picture induced urinary incontinence, dementia, and gait disturbance, he was treated with therapeutic removal of CSF, as is done in normal pressure hydrocephalus [6]. However, the treatment netted very little improvement, and per his Neurology team, will not be repeated in the future, due to the fact that his hydrocephalus is associated with his disease process, but is not directly the cause is his symptoms (as would be the case in normal pressure hydrocephalus).

In patients with intracranial amyloidosis, noncontrast T1-weighted MRI demonstrates areas of intermediate signal intensity along the leptomeningeal surfaces around the Sylvian and other cortical fissures, and over the surface of brainstem, cerebellum, and spinal cord [7], demonstrative of protein deposition. CSF analysis for this patient in 2004, demonstrated high protein levels, as can be seen in amyloidosis, as well as elevated CSF/serum albumin quotient, which is indicative of CSF-blood-barrier dysfunction, due to leptomeningeal amyloid deposition. Similar deposition may often be appreciated in the vitreous of the eyes [7]. On imaging, leptomeningeal enhancement can be appreciated with the addition of contrast, often with involvement of cranial nerves (Figs. 1–3).

Like all amyloid-mediated disease, the nature of leptomeningeal deposition is progressive. Early in the patient’s disease course, before he was diagnosed and before he began to present with recurrent seizure episodes, an MRI did not show leptomeningeal enhancement or ventriculomegaly at all. However, upon 2016 presentation, his MRI showed new hydrocephalus and worsening leptomeningeal amyloid deposition (Fig. 4).

For intracranial amyloidosis, magnetic resonance imaging is the modality of choice [8,9], due to its utility in visualizing leptomeningeal enhancement. However, amyloidosis is systemic, thus computed tomography shows utility for extracranial manifestation and staging. As it did in this patient, axial chest or neck CT scan may demonstrate lung involvement (though, of note, pulmonary amyloidosis is more often localized, than it is a part of a wide-spanning disease process) [10]. Pulmonary findings on noncontrast CT are typically nonspecific, including calcified mediastinal lymphadenopathy, patchy ground-glass appearance, and individual calcified parenchymal micronodules [9,11] (Fig. 5).

Of interest in this patient, multiple nodules are seen throughout the lung parenchyma, while the lung bases are relatively spared (Fig. 6). This sparing is not a documented typical characteristic of pulmonary amyloidosis [9].

Tracheobronchial amyloidosis primarily occurs in localized isolation, with lesions that may imitate a tracheal tumor [10]. Neck CT may demonstrate, as in this patient, multiple endotracheal and endobronchial lesions which, when biopsied, will display amyloid-characteristic staining [10,12]. This patient had a laryngeal mass removed 9 years before his 2016 hospitalization. The mass itself was histopathologically confirmed to be a squamous cell papilloma, with no amyloid staining-characteristics, however adjacent to it were additional areas of nodularity, which were attributed to amyloidosis (Fig. 7).

Teaching points

• In the brain, oculoleptomeningeal amyloid deposition produces leptomeningeal enhancement on contrast-enhanced and noncontrast-enhanced T1 MRI, seen primarily within sulci and cisterns. Leptomeningeal disease may also be evident along the surface of the spinal cord.
• Magnetic resonance imaging is the modality of choice for leptomeningeal amyloidosis and all intracranial amyloidosis.

Fig. 7 – Neck CT demonstrates multiple airway nodules, including within the glottic larynx (yellow arrow) and along the anterior margin of the upper trachea (green arrow). Papilloma is also shown (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
• Leptomeningeal enhancement is a nonspecific finding (confounding diagnoses include sarcoidosis, leptomeningeal carcinomatosis, meningitis, and others). The particular combination of recurrent presentation with acute neurologic symptoms including seizure, possibly with sensorineural hearing loss, as well as hydrocephalus, leptomeningeal enhancement, and protein-rich aseptic CSF, may prompt consideration of this uncommon entity, particularly in appropriate family history.
• Neck and thorax computed tomography offer utility for disease progress, by demonstration of amyloid deposition extracranially.
• The definitive diagnosis of any amyloidosis remains tissue biopsy with staining, showing the characteristic appearance of amyloid.

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