Cerebral Amyloidoma Accompanied by Sjögren’s Syndrome: A Case Report and Literature Review

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Abstract
We present a 69-year-old woman with colorectal cancer and a left frontal lobe tumor that was diagnosed as a cerebral amyloidoma after surgical resection. Further postoperative systemic evaluation revealed another amyloidoma in her hip as well as Sjögren’s syndrome. Systemic amyloidosis was not present. To the best of our knowledge, this is the first case of cerebral amyloidoma presenting as one of the multiple localized amyloidomas accompanied by Sjögren’s syndrome. We also present a systematic review of 65 cerebral amyloidoma cases reported in the literature over the past 40 years and discuss patient characteristics and pathological and imaging findings associated with prognosis.

Keywords: cerebral, intracranial, brain, amyloidoma, Sjögren’s syndrome

Introduction
Amyloidosis is a group of diseases that results from the abnormal, extracellular deposition of amyloid, a fibrillar protein derived from various precursor proteins that self-assemble with highly ordered normal cross β-sheet conformation. Amyloid can aggregate in organs and may cause damage. Cerebral amyloid deposition can take many forms, including cerebral amyloid angiopathy, senile plaques in Alzheimer’s disease dementia, and deposits seen in the spongiform encephalitides of Kuru, Gerstmann–Straussler syndrome, and Creutzfeldt–Jacob disease.

In rare cases, amyloid can form a tumor-like mass known as amyloidoma. Amyloidoma is commonly found in the bladder, larynx, tonsils, skin, and lungs.1) Cerebral amyloidoma is extremely rare, and only a few dozen cases have been reported. Furthermore, there have been no reports of cerebral amyloidoma with amyloidoma of another organ. In this report, we present, to our knowledge, the first case of a patient with cerebral and cutaneous amyloidomas comorbid with Sjögren’s syndrome.

Case Report
A 69-year-old Asian woman underwent head computed tomography (CT) as part of a preoperative evaluation for colorectal cancer surgery. The examination revealed a high-density left frontal lobe mass measuring 1.0 cm × 0.9 cm × 1.2 cm with inhomogeneous calcification (Fig. 1A). Magnetic resonance imaging (MRI) showed a cortical mass with iso- to low signal intensity on T1-weighted imaging (Fig. 1B), low intensity on T2-weighted imaging (Fig. 1C), low intensity on diffusion-weighted imaging (Fig. 1D), low intensity on susceptibility-weighted imaging (Fig. 1E), and little gadolinium enhancement (Fig. 1F). Neither edema nor mass effect was seen in the surrounding brain.

The patient’s colorectal cancer was diagnosed as stage IVa (T3N0M1a). Fluorodeoxyglucose-positron emission tomography before surgery showed no obvious lesions other than the primary rectal mass and two metastases to the upper lobe of the right lung. She underwent surgery for her colorectal cancer and pulmonary metastases and received postoperative chemotherapy. Pathological examination confirmed the resected tumors as adenocarcinoma. After treatment, her performance status score was zero and her disease remained controlled without recurrence. Because her cancer prognosis appeared good, we decided that surgery was...
indicated for the intracranial mass lesion. Our differential diagnosis included oligodendroglioma, dysembryoplastic neuroepithelial tumor, and colorectal cancer metastasis.

We performed an *en bloc* resection of the tumor, which was white, hard, and non-hemorrhagic with well-demarcated margins (Fig. 2A). Histological examination of the tumor showed an eosinophilic material component and another less cellular one (Fig. 2B and 2C). Verhoeff’s elastic stain showed elastic fibers (Fig. 2D). Direct fast scarlet (DFS) stain was positive for eosinophilic material with apple-green birefringence under polarized light microscopy, which indicated amyloid deposition (Fig. 2E and 2F). The KMnO₄ method distinguished the amyloid as light chain type. The final pathologic diagnosis was amyloidoma.

Subsequent systemic evaluation revealed a cutaneous amyloidoma in her hip. Although no purpura characteristic of light chain amyloidosis was observed, there were areas of pigmentation in the sacral region and right buttock; biopsy of these sites was consistent with amyloid deposition. However, serum protein electrophoresis and Bence–Jones protein urine testing were negative. A bone marrow biopsy was normal without evidence of lymphoma, multiple myeloma, or systemic amyloidosis. Serum SS-A antibody testing and the Saxon test were positive, which indicated coexisting Sjögren’s syndrome. Her final diagnosis was multiple localized amyloidomas accompanied by Sjögren’s syndrome. Over 1-year follow-up, she has remained symptom-free without recurrence.

**Discussion**

**Literature review**

We searched the PubMed database using the terms “cerebral amyloidoma,” “intracranial amyloidoma,” and “brain amyloidoma” and found 65 cerebral amyloidoma case reports published between 1981 and 2020. A summary of our review of these case reports is presented below.²–⁵¹
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Baseline characteristics

Mean patient age was 51.4 years (range, 15–87). The clinical presentation of cerebral amyloidoma was non-specific and depended on the location of the mass. Generally, symptoms included seizure (35%), hemiparesis (24%), headache (18%), and cognitive decline (8%). Cerebral hemorrhage was seen in only three patients. Diagnosis of cerebral amyloidoma prior to obtaining pathological findings is difficult, and all reported cases were diagnosed by biopsy, surgical resection, or autopsy.

The pathological diagnosis of cerebral amyloidoma is described as amyloid protein deposition which shows apple-green birefringence under polarized light with Congo red or DFS staining. The KMnO₄ method distinguished most of the previously reported cases as light chain λ type (86%). Half reported plasma cell or B-cell aggregation around the amyloid protein. Bray et al. and Laeng et al. suggested that amyloidomas appear to be burned-out extramedullary plasmacytomas that deposit amyloid proteins and proposed that the plasma cells or B cells surrounding the amyloid deposits may be related to amyloidoma prognosis.¹⁵,⁴⁹

Imaging features

Cerebral amyloidoma was generally located in the supratentorial region, particularly in the periventricular white matter (69%), where cerebral lymphoma frequently occurs. Single lesions (65%) were approximately twice as common as multifocal lesions (35%). Non-enhanced CT showed a hyperdense area in most cases (94%); calcification was seen in some (41%).

The reported MRI characteristics of cerebral amyloidoma vary. These lesions can be hypointense, isointense, heterogeneous, or hyperintense on both T1- and T2-weighted imaging. Variable accumulation of the amyloid protein⁴⁰ and dense amyloid protein deposition may be the cause of this variability.¹² Little or no mass effect was associated with 64% of amyloidomas and about half exhibited perifocal edema (45%). Gadolinium-enhanced T1-weighted imaging generally showed faint or intense peripheral or heterogeneous enhancement (96%). Peripheral enhancement may be related to amyloid deposition in blood vessel walls and disruption of the blood–brain barrier.⁵¹ In some cases, fine, irregular, radiating signal intensities with a linear pattern surrounding the tumor were observed (22%); this characteristic is thought to correspond to amyloid deposition along blood vessel walls, probably in small-sized arteries.¹⁰,¹²,²⁰,⁵¹,⁵²

Among the 66 reported cases, 52 included follow-up after surgery, excluding autopsy cases. Among these, although most had a benign clinical course (81%), recurrence or clinical progression occurred in 10 (19%). Excluding the cases with unavailable data, we compared the entire disease group (Group A) with the 10 patients in the poor prognosis group (Group B) with respect to imaging and pathological findings and surgical intervention. Group B patients tended to have multiple lesions, exhibit hyperintensity on T2-weighted imaging, and undergo biopsy. In Group A, the number of lesions was reported in 39 cases; 14 of these were multiple (36%) and 25 (64%) were single. Clinical progression occurred in 50% (7/14) of the multiple lesion group but only 8% (2/25) of the single lesion group. Lesion

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number was reported in 9 Group B patients and 7 (78%) had multiple lesions.

In Group A, T2-weighted imaging was reported in 27 cases. Eleven of these (41%) exhibited hyperintensity and 16 (59%) exhibited hypointensity, isointensity, or heterogeneous intensity. Clinical progression occurred in 45% (5/11) of the hyperintensity group but only 13% (2/16) of the other signal intensity group. Seven Group B cases reported T2-weighted imaging; 5 (71%) exhibited hyperintensity and 2 (29%) exhibited hypointensity, isointensity, or heterogeneous intensity.

Less than half of the reports reported tumor size. Average maximum diameter was 3.79 cm for Group A and 5.93 cm for Group B (3 cases). In Group B, even in cases where the size was not reported, the lesions were relatively large (e.g., a lesion that involved two lobes). Therefore, size may also be a factor that predicts clinical progression.

White matter lesions, T1-weighted imaging, peripheral edema, mass effect, radiating signal intensities with a linear pattern surrounding the tumor, and gadolinium contrast findings were also examined but did not differ between Group A and Group B. Although we examined pathological findings regarding the plasma cells or B cells around the amyloid deposits, it seemed unlikely that this factor was significantly involved in clinical progression.

Surgical procedure was reported in 52 Group A cases: 24 (46%) underwent surgical resection and 28 (54%) underwent biopsy. In Group B, surgical procedure was mentioned in all 10 cases: 1 case (10%) underwent resection and the remaining 9 cases (90%) were biopsied. The lesion progressed in 24% of the patients who underwent biopsy but in only 4% of patients who underwent gross total or partial resection. If possible, excision may be an effective intervention; however, most cerebral amyloidomas are located in the periventricular white matter (69%), which makes surgical resection difficult.

In most cases, additional postoperative treatment was not administered and the clinical course was benign (82%). However, some patients received adjuvant therapy after biopsy, including steroids, radiation, and chemotherapy (rituximab, high-dose methotrexate). Ninety percent of these patients experienced a stable clinical course. In fact, several reports concluded that radiation is an effective treatment for amyloidoma.1,39 All patients who received steroids experienced a stable clinical course (100%).

Localised multifocal amyloidomas accompanied by Sjögren’s syndrome

There are a few reports of Sjögren’s syndrome with localized multiple amyloidomas.1,53,54

In primary Sjögren’s syndrome, chronic antigenic stimulation of target organs may cause clonal expansion of B cells and neoplastic proliferation. In other words, primary Sjögren’s syndrome is considered to be a disease that may bridge autoimmune diseases and B-cell tumors. It has been reported that in cases of primary Sjögren’s syndrome under long-term observation, there is a high incidence of B-cell tumors and related diseases.54

Our review showed that there were 31 case reports that had plasma cells or B cells around the amyloid deposits. B cells affected by some antigen in the brain may acquire a monoclonality and create an antibody. Then they affect precursor proteins, which coalesce into an amyloid nodule. Subsequently, plasma cells are burned out, and the amyloidoma becomes a stable disease.10,45,49

This case is the first report of multifocal amyloidoma, including in the central nervous system.

We hypothesize that the mechanism of development of cerebral amyloidoma is not only due to the local reaction of the B-cell response to antigens in the brain, as described above, but also to the acquisition of monoclonality somewhere in body. These B cells may have crossed the blood–brain barrier and caused amyloid aggregation in the brain.

Reported cases of cerebral amyloidoma were all localized amyloidosis and none were related to systemic amyloidosis. However, a large case series on localized amyloidosis showed that 1% of cases progressed to systemic AL amyloidosis.31 These few cases of progressed systemic amyloidosis tended to have circulating monoclonal proteins or detectable clonal markers in the serum.31

Nearly one-third of patients with systemic AL amyloidosis die within a few months of diagnosis.55 Survival of systemic AL amyloidosis has been significantly improved by the availability of new chemotherapeutic agents, but challenges remain regarding the treatment of advanced disease and early diagnosis is the key to better outcomes.55 Therefore, although it is rare, even in a case of cerebral amyloidoma, systemic amyloidosis should be ruled out.

**Conclusion**

Our case was of a 69-year-old woman presenting with multiple localized amyloidomas with comorbid Sjögren’s syndrome. In all, 66 cases of cerebral amyloidoma were included in our systematic review. This review showed that there were no previous cases of cerebral amyloidoma associated with systemic amyloidosis. The case presented here shows that amyloidoma can progress to systemic amyloidosis, so a systematic work-up and long-term follow-up are necessary.
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Conflicts of Interest Disclosure

The authors declare no conflicts of interest associated with this article.

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