Massive Intracerebral Immunoglobulinoma: A Case Report and Review of the Literature

Written by Petra Houbova, 2015 Student Delegate, University of Maryland, and R. Castellani

Patient Presentation:
A 31-year-old man presented to the emergency department with worsening, temporary drops in visual acuity over 5 months, but was otherwise healthy. Left-sided exotropia was the only positive finding on physical examination. Routine serum chemistries were unremarkable. The patient was admitted to the hospital for imaging and further workup.

Hospital Course:
A brain MRI revealed at least six extensive mass lesions located predominantly in the white matter of the supratentorial compartment. The lesions were well-demarcated, with homogenous, intermediate signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and hypointensity on T1-weighted images. There was gadolinium enhancement of vessels running through the masses, but no enhancement of the lesions. The largest lesion measured 7.7 x 7.4 x 5.5 cm (transverse x anteroposterior x craniocaudal), occupying most of the white matter of the inferior aspect of the left frontal lobe, including the left frontal operculum, and extending to the anterior body of the corpus callosum. The second largest lesion, measuring 5.0 x 4.4 x 4.5 cm, occupied the posterior body of the corpus callosum with exophytic extension into the lateral ventricles (Figure 1). Numerous smaller lesions, all in the subcortical white matter, were also observed in the superior paramedian right occipital lobe, posterior left frontal lobe, and inferior posterolateral left temporal lobe. Cerebral ventricular architecture was greatly distorted. Lesions occupied a significant portion of ventricular spaces, with dilatation and entrapment of the right lateral ventricle and dilatation of the inferior aspect of the third ventricle. Marked mass effect was seen, with complete effacement of the cerebral sulci and the suprasellar, ambient, and basal cisterns. An MRI of the brain was unremarkable apart from the aforementioned abnormalities.
A craniotomy with resection of the left frontal mass was performed. The patient recovered from the surgery neurologically intact. Follow-up scans after one year showed no significant increase in the extent of the lesions.

Pathology Findings:
The resected lesion consisted of an aggregate of fragments ranging from pink-tan to white-gray and gelatinous to granular, with admixed white matter. A sample of the mass was submitted for analysis.

Hematoxylin and eosin stain showed widespread perivascular, extracellular, amorphous, eosinophilic, proteinaceous material. At the periphery of the lesion, adjacent to normal-appearing vessel walls, a mild lymphoplasmacytic infiltrate was noted (Figure 2). Immunohistochemistry showed a mixed population of B- and T-lymphocytes (CD4 and CD20 immunostain positive, respectively), as well as occasional plasma cells (CD138 positive) within the infiltrate. The amorphous material was negative for Congo red, thyroglobulin, and β amyloid. Electron microscopy revealed amorphous granular material amongst scattered endothelial cells and collagen, with no fibrillary amyloid (Figure 3).
Figure 2: Hematoxylin and eosin stain shows widespread extracellular deposits of amorphous eosinophilic material. A modest leukocytic infiltrate surrounds vessels running through the mass.

Figure 3: Electron micrograph (4000x) of the deposited material (star) amongst scattered collagen (C) and an endothelial cell (arrow). The deposition is amorphous and granular, with no evidence of fibrillary structures.

Since the Congo red stain was negative, and no fibrillar aggregates were identified on ultrastructural examination, the amorphous material was unlikely amyloid. Liquid chromatography mass spectrometry was used to identify any protein components. The sample was found to contain κ immunoglobulin constant and variable light chains (LCs), and α immunoglobulin heavy chain (HC).

**Diagnosis:**
Massive cerebral accumulation of immunoglobulin.

**Discussion:**
While intracerebral proteinaceous accumulations themselves are not a particularly rare occurrence, the collective findings in this case are unprecedented in the medical literature. Many proteins have been found to aggregate intracerebrally, including prion protein, amyloidogenic proteins (such as amyloid β), tau protein, transthyretin, gelsolin, and polyglutamine. Cerebral deposits of the various proteins are associated with both
benign (e.g., the normal process of aging) and pathologic entities (e.g., Creutzfeldt-Jakob disease, Alzheimer disease, Parkinson disease, Huntington disease, and others). The present case involves the deposition of immunoglobulin (Ig) components. Ig and Ig component deposits have been observed in a number of morphologic variants both intra- and extracellularly: globules, crystals, amorphous or organized aggregates or gels. Additionally, they can be classified as being amyloidogenic or non-amyloidogenic. Amyloid is an insoluble aggregate of misfolded proteins in characteristic β-pleated sheets, which appear as fibrils on electron microscopy. It is Congophilic. Amyloidogenic Ig is most commonly reported to be of the λ LC isotype. In contrast, non-amyloid deposits are amorphous, ultrastructurally disorganized, Congophbic, and more likely to be composed of κ LCs if LCs are present. Both amyloid and non-amyloid deposits are associated with respective clinical manifestations: amyloid with amyloidosis, and non-amyloid with deposition diseases, categorized as light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), or light and heavy chain deposition disease (LHCDD).

Localized intracranial Ig deposition, as in the present case, is exceedingly rare. Of the two types, amyloidogenic Ig deposits are more frequently reported and less variable in their characteristics than non-amyloidogenic Ig deposits. They have been described as isolated mass lesions, mostly in the white matter, composed of λ LCs, and dubbed amyloidomas due to their tumor-like presentation on imaging. These lesions are always contrast enhancing, implying a breakdown of the blood brain barrier.

To the authors’ knowledge, and excluding the present case, only fourteen intracranial non-amyloid proteinaceous deposits have been described in the literature. There are markedly less consistent characteristics between cases. Some of the lesions were contrast enhancing and some were not, and nearly every accumulation was composed of a unique combination of HCs, LCs, and other proteins. In terms of morphology, three of the fourteen cases featured eosinophilic aggregates in a more diffuse configuration: perivascular distribution, within vessel walls, and around lymphocytic infiltrates. The remaining eleven published patients presented with tumor-like masses in cerebral and/or cerebellar white matter, eight with single, and three with multiple masses. In two cases, extracellular crystal deposits were observed in addition to the mass lesions.

Due to the small number and heterogeneity of documented cases of localized intracranial LC aggregates, the specific conditions leading to their formation and morphology remain unclear. Plasmacytic tumors such as multiple myeloma, monoclonal gammopathy of undetermined significance, lymphoplasmacytic lymphoma, plasmacytoma, or B-cell lymphoma are known to produce an excess of Ig and Ig components. Their aggregates are clinically associated with amyloidoses, LCDD, cryoglobulinemia, or crystal-storing histiocytosis, among other disorders. Seven of the fourteen cases were confirmed to be associated with a plasma cell dyscrasia or a disorder of plasma cells. A single case was associated with chronic inflammation. The remaining six documented cases had insufficient evidence, or absence of evidence, of a plasmacytic tumor or other pathologic process. In the present case, no evidence of monoclonal gammopathy, plasma cell dyscrasia, or lymphoma was noted after two years of follow-up.

In light of the lack of significant underlying pathology, the number and size of the lesions in the present case is even more remarkable. Of the published cases of localized
intracranial non-amyloid LC deposits, only three presented clinically as multiple masses, with the rest presenting as single lesions or diffusely distributed aggregates \(^4\)-\(^10\). Of the three multiple mass lesions, two were attributed to marginal zone lymphoma, and the remaining was suspicious of and consistent with crystal-storing histiocytosis \(^4\).

Conceivably, the patients described in the three cases presented with significant functional impairment. In the present case, pronounced physiological manifestations were conspicuously absent.

In summary, we report a case of massive intracerebral accumulation of immunoglobulin, to an extent previously undescribed in the literature. Also noteworthy were the subtle clinical signs, the limited disease progression over time, and the absence of an underlying plasma cell dyscrasia. The precise source of the immunoglobulin, and overall pathogenesis of this process, is unclear.

References: