

# Pituitary Prolactinoma with Amyloid Deposits: Surgery or Dopamine Agonists? Review of Previous Reports and New Recommendations for Management

## Abstract

**Background:** Pituitary adenomas, macro and micro, are a common occurrence in most neurosurgical centers. Prolactinomas are the most common pituitary tumors and are often treated nowadays with dopamine agonists such as cabergoline, with good results. **Aims and Objectives:** To suggest new therapeutic guidelines for treating Prolactinomas with Amyloid deposits on preoperative detection of Amyloid deposition in Pituitary tumors, based on MRI characteristics. **Materials and Methods:** We report a case of a pituitary prolactinoma with amyloid deposits in a 45-year-old male who underwent a transsphenoidal excision of the adenoma. Although on magnetic resonance imaging scans, no amyloid was reported, at histopathology, spherical amyloid within the pituitary tumor was found in abundance. The patient underwent surgery without any trial of cabergoline due to rapid deterioration of vision. **Conclusion:** Prolactinomas with amyloid deposits are known not to respond to dopamine agonists (cabergoline) by a reduction in size and may, in fact, increase in volume. Therefore, we recommend that in prolactinomas not responding to medical therapy, deposition of amyloid has to be considered as a cause for failure of medical therapy and surgery and then has to be offered pronto.

**Keywords:** Amyloid, cabergoline, prolactin, pituitary tumor

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## Introduction

Amyloid deposition is well described to occur in pituitary tumors. This is commonly seen in prolactinomas but rarely in growth hormone (GH) and adrenocorticotrophic hormone-secreting and nonfunctional adenomas.

The cause for this has been suggested to be abnormal processing of hormone or prohormone by the adenoma cells, and this is the origin of the spherical amyloid formation.

Amyloid in pituitary tumors is difficult to diagnose on magnetic resonance imaging (MRI) before their excision as till recently, there were no imaging characteristics of amyloid described, either on computed tomography or MRI scans.

It is known that prolactinomas with amyloid deposits do not shrink on dopamine agonist therapy, and in fact, may enlarge. Hence, administration of cabergoline may

enlarge these tumors necessitating immediate surgery.

We report a case, where in a prolactinoma; the MRI did not suggest amyloid deposit. The tumor was removed surgically as patients vision was in jeopardy. Histopathology was a surprise showing spherical amyloid deposition.

We recommend that prolactinomas with amyloid deposition diagnosed on MRI preoperatively should be directly removed surgically without trying to treat it with cabergoline.

## Materials and Methods-Case Report

A 45-year-old male came with painless progressive rapid loss of vision in both eyes, first on the left and then on the right, of 3 months duration. At presentation, he had no perception of light on the left and perception of movements on the right. Apart from bilateral primary optic atrophy, the patient had no other neurological deficits. There were no hormonal symptoms reported by the patient.

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MRI brain showed a large 3.5 cm × 4 cm sellar, suprasellar enhancing mass with areas of hypointensity, suggestive of a pituitary macroadenoma causing severe compression of the optic chiasma and both optic nerves. The well-capsulated lesion showed heterogeneous intermediate to minimally hyperintensity on T2 images and isointensity on T1 images. Inhomogeneous hypointense areas on GRE sequence suggested hemorrhages/calcification. Small irregular cystic areas were seen along its superior periphery on T2-weighted images. Mild-to-moderate volume loss of both optic nerves suggestive of optic atrophy was noted. The tumor extended superiorly up to the hypothalamus, involved the cavernous internal carotid artery bilaterally, and inferiorly encroached into the sphenoid sinus [Figure 1a and b].

Hormonal evaluation showed low T3–T4 levels with lowered thyroid-stimulating hormone level indicative of pituitary hypothyroidism and low serum cortisol levels, and serum prolactin (PRL) level was above 2000 ng/mL indicating severe hyperprolactinemia.

In view of impending blindness, it was decided to not opt for cabergoline therapy and to proceed immediately with surgical removal of tumor to decompress the optic apparatus.

Accordingly, after initiating thyroid and cortisol replacement therapy, the tumor was removed microsurgically by the transsphenoidal route using neuronavigation guidance [Figure 2].

At surgery upon opening the sellar dura, the soft tumor extruded and had a few areas of intralesional hemorrhages. Despite Valsalva maneuver, some tumor stuck to the hypothalamus and cavernous sinuses did not descend and was, hence, left behind. Postoperative MRI showed a substantial excision with a small suprasellar residue [Figure 3].

Histopathological examination showed tumor cells arranged in sheets with scant stroma in between [Figure 4]. The stroma in areas showed extracellular spherical pink amorphous acellular material. Sections were stained with Congo red and examined under polarizers. They revealed apple-green birefringence confirming that the pink material was amyloid [Figure 5].

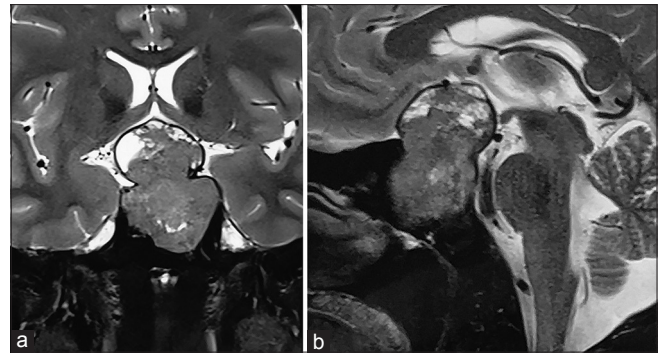
Postoperatively vision on the right improved substantially, but on the left showed only marginal improvement with the perception of hand movements at 3 feet.

At follow-up, 6 months later, his vision had further improved to 6/6 on the right and only slightly on the left.

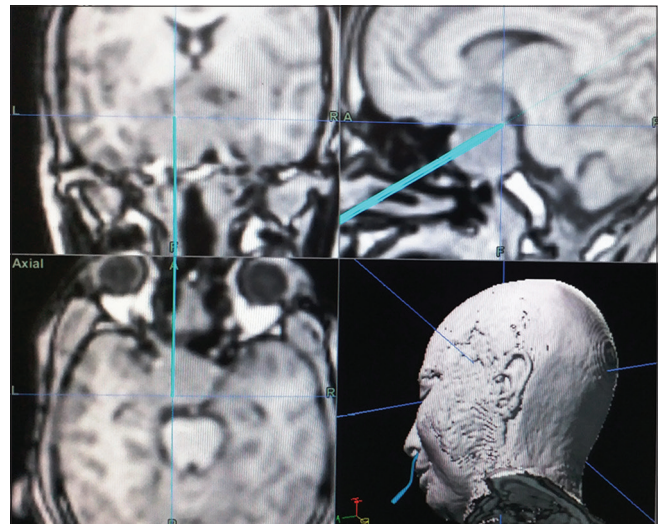
His residue is being observed on MRI to decide about adjuvant therapy.

## Discussion

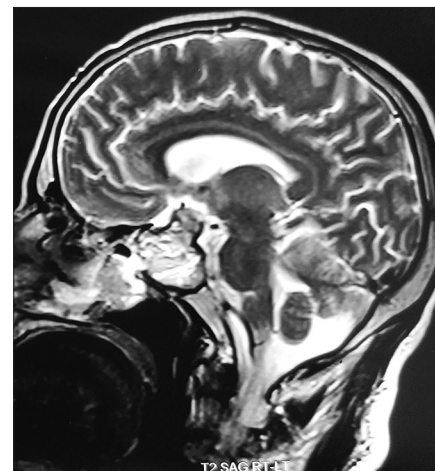
Amyloid has been reported to be present in different tissues: the liver, spleen, kidney intestines, and in



**Figure 1:** (a and b) Preoperative magnetic resonance imaging T2-weighted coronal and sagittal images showing heterogeneous isointensity with cystic areas extending superiorly to the hypothalamus and descending into sphenoid sinus



**Figure 2:** Neuronavigation intraoperative snapshot at the end of excision



**Figure 3:** Postoperative T2 magnetic resonance imaging showing large excision with small superior residue and fat chiasmopexy below

endocrine organs such as the pancreatic islets of Langerhans, thyroid, and pituitary gland. Amyloid deposition is commonplace in neoplastic endocrine tissues secreting peptides, all over the body. Hyaline



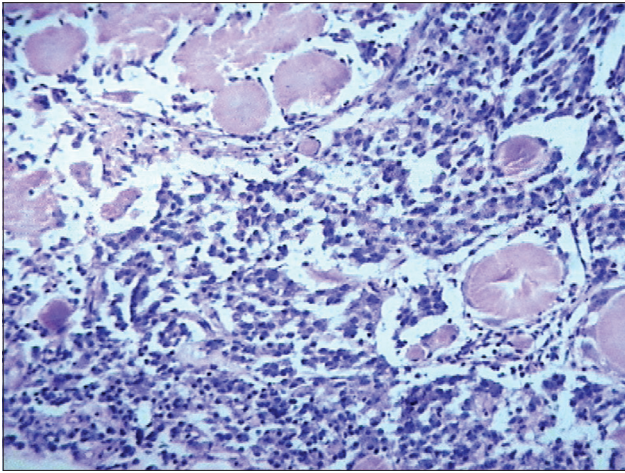


Figure 4: HP slide Microphotograph of tumor with masses of spherical, laminated eosinophilic amyloid material (H and E)

bodies which were interpreted to be due to progressive degeneration of adenoma cells were first reported by Ribbert in 1882. Barr and Lampert were the first describing, with uncertainty, the presence of pituitary neoplasm bodies composed of amyloid.<sup>[1]</sup> Still, it was not until 1983, when a PRL-secreting pituitary adenoma was proven to contain the amyloid substance.<sup>[2]</sup>

Several types of amyloid deposition has been described in pituitary tumors, the sellate or perivascular type is seen in all endocrine types of pituitary tumors and is characterized by fibrillary or crystalloid microstructure and is found deposited around blood vessels, whereas the spherical type which is rare, occurs exclusively in PRL-secreting tumors and has many coral-like spheroid accumulations with variable diameters (40–150  $\mu$ ).<sup>[3,4]</sup>

Amyloid deposits are caused by twisted beta-pleated sheet fibril accumulation forming micellar structures of  $\beta$ -protein.<sup>[5]</sup> Amyloid fibril proteins are known to be fragments of larger protein precursors.<sup>[6]</sup> Synthetic peptides of PRL can form amyloid fibrils *in vitro*.<sup>[7]</sup> Electron microscopy shows nonmembrane-limited fibrils in neoplastic cells in a prolactinoma with spherical amyloid bodies, suggesting that these intracellular fibrils are the intracellular source of amyloid. Spherical amyloid deposits in prolactinoma are generally positive for PRL in immunohistochemical staining as in our case.<sup>[8]</sup> Further, amyloid deposition in pituitary adenoma has been associated with local conditions, suggesting that the amyloid fibrils are produced by adenoma during degeneration.<sup>[6-8]</sup> Bakhtiar *et al.*<sup>[9]</sup> suggest that deposition of amyloid may be related with the PRL synthesis process and may be enhanced by a naturally developed degenerative change in a prolactinoma. Another possibility is that mesenchymal histiocytes produce the amyloid by unknown processes, and the accumulation is enhanced by dopamine agonist therapy.<sup>[2,4,8]</sup>

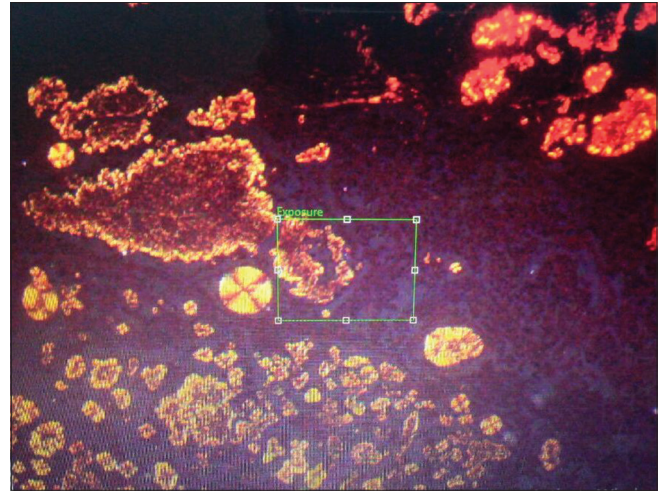


Figure 5: HP microphotograph of tumor Congo red staining showing apple-green birefringence under polarized light

Hinton *et al.* characterized the spherical amyloid protein from a prolactinoma and demonstrated on electrophoresis that it is a band of approximately 4 kDa peptide composed of N-terminal amino acids 1–34 of PRL.<sup>[10]</sup>

Localized endocrine amyloid deposits, as those seen in the pituitary gland, are also termed amine precursor uptake and decarboxylation amyloid, because the cells that secrete it share the property to handle the precursor of biogenic amines,<sup>[3]</sup> these deposits may be different from amyloid in other endocrine tissues.<sup>[11]</sup>

Dopamine agonists such as bromocriptine and cabergoline have now changed the treatment of symptomatic prolactinomas. In approximately 66% of patients, tumor size is reduced, especially in those with large tumors.<sup>[8]</sup> Treatment with bromocriptine has been associated with extensive tumoral fibrosis and amyloid formation.<sup>[9,12]</sup>

The pathologic findings in our case reveal the rare type of nodular or spheroid amyloid deposit, which consists of an accumulation of amorphous spheres. Microscopic examination showed that the spheres had multilayered concentric substructures that were surrounded by areas containing adenoma cells. Spheroid-type amyloid-containing pituitary adenomas are usually confirmed to be PRL-producing adenomas.<sup>[3,11]</sup>

Only 30 cases of histologically proven spherical amyloid bodies in pituitary adenoma have been reported until 2013 in the literature.<sup>[12]</sup> All tumors were prolactinomas except one GH-producing adenoma. Most of these cases are reported by neuropathologists or neuroradiologists from their nonclinical perspective and only one by a neurosurgeon.<sup>[9]</sup>

No further case reports have been found by us on literature search.

Treating prolactinomas with cabergoline is now the standard recommended practice, and the surgery is only

done for one of the following reasons: impending blindness or patient not willing to take cabergoline lifelong.

With high-quality MRI contrast imaging, pituitary adenomas with amyloid deposition can now be mostly diagnosed preoperatively, rather than at a histopathological examination as used to happen earlier. The characteristic appearance on MRI is with low or heterogeneous intensity on T1 and low intensity on T2-weighted images. The latter is the unique feature of amyloid deposition. Following infusion of gadolinium, there is an enhancement of the periphery but not most of the tumor mass.<sup>[12,13]</sup> These MRI characteristics are different than those of typical pituitary adenomas.<sup>[12]</sup> Amyloid deposits do not cause any characteristic clinical or biochemical features. Therefore, intrasellar amyloid deposition is difficult to diagnose preoperatively.<sup>[13,14]</sup>

The typical MRI findings now allow entertaining intrasellar amyloid deposition even preoperatively.<sup>[14]</sup>

Furthermore, administration of dopamine agonists like cabergoline has been known to increase the amyloid deposition and cause an increase in the size of the tumor instead of decreasing it.<sup>[4,13,14]</sup>

Besides, such tumors with amyloid are much less likely to reduce in size after cabergoline administration.<sup>[12]</sup> Hence, it may be in line to suggest that if one is able to diagnose amyloid deposition in a prolactinoma on preoperative imaging, especially those exhibiting mass effects on the visual apparatus, it would be best not to attempt to treat such patients with cabergoline but to proceed with surgery directly.<sup>[14]</sup> These guidelines may have new therapeutic implications.

From 2001 to 2019, 84 cases of pituitary tumors were operated at our institute mostly by the transnasal route, only one case with amyloid deposition has been diagnosed at histopathology.

Although the radiological diagnosis was not made in our case preoperatively, we proceeded with surgery immediately to save patients vision in the right eye, the left eye being already nearly blind. Our diagnosis was made after the histological report arrived. Premalatha *et al.*<sup>[15]</sup> report a similar case in 2016, where surgery was performed directly as amyloid was not diagnosed on preoperative imaging.

Thus, the recommendation and new treatment implication would be to proceed with surgery directly in a prolactinoma with amyloid deposition diagnosed on MRI scans, without attempting cabergoline therapy.

## Conclusion

Pituitary prolactinomas are commonplace, but ones with spherical amyloid deposition are extremely rare. Using dopamine agonists in a prolactinoma with amyloid deposits may not only result in failure to shrink the tumor but

also may cause enlargement and fibrosis of the tumor leading to greater excisional difficulties during subsequent surgery. Hence, proceeding directly with surgery without administering cabergoline, may be the best therapeutic option for such patients.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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