

Case Report of a Pituitary Macroadenoma Treated With Artemether

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Introduction: This report describes the case of a male patient with pituitary macroadenoma treated with the artemisinin analog artemether. **Patient and Methods:** A 75-year-old male patient presented with vision, hearing, and locomotion-related problems. Artemether was administered orally to the patient over a period of 12 months. **Results:** Although the tumor remained consistent in size, CT scan shows a reduction in its density, and clinically, the related symptoms and signs resolved significantly as therapy progressed. **Discussion:** Overall, the artemether treatment was beneficial in improving the patient's quality of life. Artemether and other artemisinin analogs offer promise for cancer therapy.

Keywords: artemether; artemisinin; pituitary gland; microadenoma; cancer; apoptosis

The pituitary gland is about the size of a pea and sits in a small, bony cavity (sella turcica) at the base of the brain. Pituitary adenomas are benign neoplasms arising from the cells of the pituitary gland. There are 3 types of adenomas, classified mainly based on size: microadenoma (less than 10 mm in diameter), macroadenoma (more than 10 mm in diameter), and giant adenoma (more than 40 mm in diameter).¹ Although such tumors are common (found in up to 10% of those with normal endocrine function), the actual prevalence is not known, as most are asymptomatic.² They are found in up to 27% of patients upon autopsy.² Most adenomas do not metastasize and remain confined to the pituitary and surrounding tissues. Pituitary adenomas can be associated with either hypersecretion/hyposecretion of various endocrine hormones (functional) or mass/space-occupying effects (nonfunctional). Very little is known about the etiology of such tumors. They most likely arise due to monoclonal neoplastic transformation of pituitary cells.³ Alterations in the pituitary tumor-transforming gene and the *gsp* oncogene have been implicated.¹ Most treatment for any clinically significant adenomas involves surgery, radiotherapy, or medications. In the case of a macroadenoma, surgery (often combined

with radiation) is the most common treatment option. Treatment of adenomas with surgery alone is associated with a 9% risk of significant complications other than hypothyroidism.⁴ Additionally, there is a significant recurrence risk with surgical treatment alone. Park et al found a 5-year recurrence rate of 15.2% and a 10-year recurrence rate of 50.5% for 132 patients having nonfunctioning macroadenoma who were followed up after treatment by surgical resection alone.⁵ Dekkers et al found an approximately 10% recurrence in 99 patients having surgical resection of nonfunctioning macroadenomas after a 6-year follow-up.⁶ A combination of surgery and radiotherapy results in a progression-free survival rate of up to 86% in adults.⁴ Recurrence of tumor (recurrence of visual symptoms) and/or increase in tumor size have been reported in approximately 20% of adults following combined radiation and surgery treatment.⁷ Although mortality from such tumors is low (adenomas of the pituitary gland are usually slow-growing and do not metastasize), adenomas can cause significant morbidity owing to local invasion³ by compressing important surrounding structures in the brain including optic nerves.

In this case report, we have implemented a novel therapy for a pituitary tumor using artemether, an analog of the antimalarial drug artemisinin. Artemisinin is a sesquiterpene lactone usually extracted from the plant *Artemisia annua* L. (sweet wormwood). The artemisinin molecule contains an endoperoxide bridge that reacts with an iron atom to form free radicals⁸ that cause macromolecular damage and cell death. Since cancer cells have a significantly higher iron influx via the transferrin receptor mechanism, they are more susceptible to the cytotoxic effect of artemisinin. The anticancer potential of artemisinin analog dihydroartemisinin has been studied in vitro with promising results.^{9,10} Artemether has also been shown to be safe

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in animals and humans at higher doses than used here.¹¹⁻¹⁴

Patient and Methods

The patient is a 75-year-old retired schoolteacher residing in a rural village in North India. He is a vegetarian with no history of alcohol or tobacco use. He has had diabetes mellitus for 17 years for which he was treated with oral hypoglycemics. He had coronary bypass surgery 4 years prior to this visit. He presented at the Primary Health Center complaining of gradual loss of movements in the left eye, poor vision, and unsteady gait for more than a month, along with moderate bilateral hearing loss of insidious onset (patient could not recall the initial onset of hearing problems but estimated the course to be in years). There was no history of headache. Prior to this visit, he consulted an ophthalmologist with complaint of double vision. The ophthalmologist observed loss of acuity, medial convergent squint, and diplopia in the left eye only and suspected pituitary adenoma compressing the optic nerve (resulting in loss of acuity) and the sixth cranial nerve (resulting in convergent squint leading to diplopia). The patient then consulted his primary care physician (VKP). A CT scan with IV contrast on April 15, 2004, revealed a rounded, dense, and relatively homogenous mass (density ranging from 72 to 77 HU [Hounsfield Units] of section size 2.4 [anteroposterior diameter] × 2.6 cm [lateral diameter]) in the pituitary area of the brain. Normal measurements of an adult pituitary are 0.56 cm × 1.56 cm.¹⁵ There were no signs of apoplexy. A tentative diagnosis of pituitary macroadenoma was made. In the absence of other disease in the patient, we excluded diagnostic possibilities of tuberculosis (which often lead to pituitary masses), pituitary hyperplasia, and pituitary cryptococcoma (common in AIDS and other immuno-compromised patients). Other possibilities such as chordoma (excluded due to location), metastatic tumors (excluded due to slow rate of tumor growth in this patient and lack of metastasis elsewhere), craniopharyngeal tumor (excluded as most occur in young patients), and plasmocytoma (excluded due to its rarity) seemed unlikely. The possibility that the mass could be a lymphocytic hypophysitis was considered but ruled out on the basis that lymphocytic hypophysitis consists of inflamed lesions that strike mostly in younger females.

The patient was treated with 40 mg (approximately 0.5 mg/kg) of artemether orally daily for 29 days starting on April 16, 2004. This medication was given with milk 3 to 4 hours after dinner. Two hundred units of vitamin E (D alpha tocopherol) and 500 mg of vitamin C were given to the patient at breakfast. After 15 days of treatment, his left eyeball started moving slightly and there was a slight improvement in vision,

and this treatment was continued for 2 more weeks. Artemether therapy was then reduced and given only every other day for a duration of 30 more days. Vitamin E and C were given every day. Artemether therapy was reduced further and given twice a week for approximately 10 more months. Vitamin E and C were given every day for the entire period.

Results

A CT scan performed on August 9, 2004 (approximately 4 months after the initial diagnosis and start of treatment), showed an increase in adenoma size to 3.0 × 2.4 cm. Although there was a slight increase in size of mass, the patient's visual and other symptoms and signs had improved significantly. Another CT scan was performed on January 25, 2005 (approximately 9 months after the initial diagnosis and start of treatment). The tumor remained consistent in size measuring 3.33 × 2.25 cm. Additionally, the patient reported marked improvement in visual problems. The patient's gait had returned to normal, and his hearing had improved significantly. Also, reduced doses of oral hypoglycemics were needed for control of diabetes. The patient was more alert and active than before. A CT scan on November 15, 2005, showed no significant change in tumor size (2.6 × 2.4 cm) compared to previous CT scans. However, this scan of November 2005 did show the density of the tumor (ranging from 51 to 59 HU) significantly decreased since the first scan (72-77 HU) in April 2004. Additionally, the November 2005 scan showed the tumor had become more heterogeneous. The patient also reported a nearly complete symptomatic recovery.

Discussion

We have previously reported that dihydroartemisinin selectively killed Molt-4 lymphoblastoid cells (a human leukemia cell line) after incubation with holotransferrin,⁹ whereas the same treatment had significantly less effect on normal human lymphocytes. A similar effect was observed in human breast cancer cells.¹⁰ Furthermore, we found that oral administration of an artemisinin analog and ferrous sulfate retarded the growth of implanted fibrosarcoma tumors in rats.¹⁶ Another study has also shown that artesunate can effectively retard the growth of various types of human cancer cells *in vitro*.¹⁷ We have also previously reported a case of a laryngeal cancer patient who responded well to artesunate (an analog of artemisinin) therapy.¹⁸ A recent report has shown that artesunate was effective in the long-term treatment of metastatic uveal melanoma in conjunction with conventional chemotherapy.¹⁹

This is the first report on the use of artemether as treatment for a pituitary tumor. Artemether (an analog of artemisinin) was chosen for the treatment because it easily crosses the blood-brain barrier, and similar to dihydroartemisinin,²⁰ it kills cancer cells by apoptosis (data not shown), a preferable mode of cell death in cancer treatment. Also, it has a longer half-life compared with the more water-soluble artesunate, used previously.¹⁸

Many nonfunctioning pituitary adenomas exist asymptotically for long periods of time, detected only upon investigation for unrelated illness or on autopsy.²¹ Studies on the natural course of nonfunctional pituitary adenomas show that a majority of tumors may remain constant in size without noticeable symptoms.^{22,23} However, in a study that followed patients for only 2.7 years, 26.3% of patients with macroadenomas showed a significant increase in tumor size.²² In another study with longer follow-up periods (mean of 5 years), 40% of adenomas increased in size.²³ In the latter study, 20% of patients became symptomatic and 9.5% developed apoplexy. Thus, especially in the case of macroadenoma, early treatment of the tumor may prevent growth and complications. The patient has an increased risk of apoplexy,²³ as the tumor grows. Also, without treatment, nonfunctioning pituitary tumors can cause significant morbidity due to pressure on surrounding structures. In this case, the patient's initial visual complaints may have been due to a part of adenoma (which was not obvious on the CT scan) extending beyond the sella turcica into the surrounding structures such as the optic nerve and cavernous sinus (through which the sixth nerve passes).

In this case, a combination of surgery and radiotherapy (the most common treatment option for such tumors) was offered to the patient, but he refused. Although these treatment options are often successful, the incidence of surgical complications²⁴ and side effects from radiotherapy²⁵ were of concern to this patient.

Interestingly, though the patient reported relief of symptoms, artemether treatment did not significantly reduce the size of the tumor. Although the tumor measured approximately the same during the course of the treatment, there was a significant reduction in the density (72-77 HU in the first scan vs 51-59 HU in the last scan) and the tumor, which was initially homogeneous, appeared heterogeneous in the later scan. We speculate that the remainder of the mass may consist mostly of dead cells after the treatment. We also hypothesize that it takes a longer time, particularly in older patients, for microglia and macrophage cells to scavenge dead cells from solid pituitary tumors. This change in composition, in addition to the reduction in the density of the tumor, may account for the resolution of the

patient's symptoms. Because the possibility of optic and sixth nerve compression exists, the decreased density may have eased the pressure on these structures. The patient is currently doing well and reports normal visual functioning without any complaint of hearing or gait and has stopped artemether but continues vitamins in the dosage mentioned above. It is likely that gait problems were vision related and long-standing hearing loss may have been due to existing diabetes. Regular CT scans will be performed in the future and used to monitor his progress. We feel artemether therapy was successful in improving the quality of the patient's life. Pituitary adenomas result in severe deterioration in not only physical health but also overall quality of life.² However, the main options for treating a nonsecreting macroadenoma are invasive (transphenoidal surgery) and have significant side effects (radiation). Thus, a treatment that has minimal side effects may both improve a patient's quality of life and address these issues. We feel that this promising new artemether therapy may provide a safe and effective alternative to currently used treatments for pituitary and other cancers.

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