Case report
Radiation-induced intracranial vasculopathy after radiotherapy (laser surgery) for craniopharyngioma: a study case report

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Abstract
Brain irradiation is commonly used for many primary brain malignancies. After radiotherapy, the potential for the development of radiation-induced vasculopathy exists and should be kept in mind. Craniopharyngioma is one rare slowly developing, usually benign tumor. In the majority of cases, such tumors grow above the anterior upper lip of pituitary gland and are located mainly on Sella Turcica or on side sella areas. Macroscopically, they seem like big globe tumors with the white or red-blooded surface. Histologically, have ascertained two types, adamantinomatous and papillary type (though they have ascertained and mixed types). However, independently of their main type, they usually have cystic form. The size of craniopharyngioma is between 2 to 4 cm. Strike 0.12-2/100.000 people a year, 30 to 50% of all cases presenting during childhood and adolescence and they constitute the 2-5% of all brain tumors. The peak incidence rates have been shown in children of ages 5 to 14 years and adults of ages 50 to 74 years. The study below presents one case of post-radiation vasculopathy of the brain arteries of the patient who received radiation therapy to the brain as part of his craniopharyngioma management. It will be underscored the significance of this patient condition and also will be described possible routes to prevent the occurrence of vasculopathy.

Keywords: Cerebral vasculopathy, Radiation damage, Craniopharyngioma, Radiation therapy

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Introduction
Craniopharyngioma is a rare benign brain tumor arising along the craniopharyngeal duct and usually diagnosed during childhood or adult life with low histological grade (Hermann et al. 2014, Karavitaki et al. 2006). A plethora of patients are treated with both surgery and/or radiotherapy [Lo et al. 2016]. Radiotherapy is one of the primary treatments of brain tumors (Kralik et al. 2017). Although survival rates after removal of craniopharyngioma is 80-90% at 10 years by radioactive radiation (Habrand et al. 1999, Lo et al. 2014, Hetelekidis et al. 1993), patients with craniopharyngioma suffer potential adverse effects including hypopituitarism, visual problems, seizures, neurocognitive impairment, mood disorders (Varlotto et al. 2002, Laffond et al. 2012, Boop et al. 2012, Shiminski-Maher et al. 1990, Sterkenburg et al. 2015) and also radiation necrosis, atrophy, gliosis, telangiectasia, cavernous malformations (Wang et al. 2014). Cerebrovascular vasculopathy is also a potential adverse effect of cranial radiotherapy (Liu et al. 2009, Ayuk et al. 2012, Mueller et al. 2013, Ullrich et al. 2005). In the study of Brant-Zawadzki et al. was reported, when radiation-induced cerebrovascular vasculopathy occurs, histologically accompanying by the presence of subintimal foam cells and myointimal proliferation, fibrous thickening and hyalinization of the subintima, thickening of the elastica, fibrous thickening of the adventitia, and loose connective tissue thickening occluding the lumen (Brant-Zawadzki et al. 1980). It should also be noted that patients with a predisposition to insulin resistance, glucose intolerance, dyslipidemia, and hypertension have an increased risk of vasculopathy after radiotherapy of craniopharyngioma (Srinivasan et al. 2004). In the proposed study we report a case of a vasculopathy caused by radiotherapy of craniopharyngioma to continue for 3 years because the area of craniopharyngioma’s location is not surgically removable area. The craniopharyngioma detected for the first time by magnetic resonance imaging (MRI) due to often and intense headaches. The result of angiopathy became the automatic rupture of the vessels with the subsequent formation of subarachnoid bleeding and hematoma which together with the existing craniopharyngioma due to the pressure exerted on the basic brain structures, caused death because of cardiopulmonary failure. Thus, although radiotherapy carries a large number of degenerative changes in the surrounding highly functional areas, this method of treatment remains the best when it is not possible to perform a surgical intervention (Caldarelli et al. 2005).

Methods
The male patient was taken to the hospital with the following symptoms - often and intense headaches. Hereinafter was diagnosed with the craniopharyngioma in the pituitary area after the execution of the MRI. The maximum size of the craniopharyngioma was 2 cm. Subsequently, the patient was treated with laser for 3 years, because the craniopharyngioma was located in was not surgically removable area. The irradiation of the area caused postoperative metacentric vasculopathy and in combination that the patient suffered from hypertension, occurred the automatic rupture of the vessels and the formation of subarachnoid bleeding and hematoma.
Probably the bleeding started intraparenchymally, in the area where the tumor was previously located. Mild brain edema also was reported. Regarding the symptomatology, the patient was observed visual disorders and breathlessness, for around 3-4 days before his death. Eventually, the cause of death was a cardiopulmonary failure due to pressure on the basic brain structures.

Results
Notwithstanding craniopharyngioma was treated with radiation therapy, three years after it initiated, the patient developed vasculopathy, which led to the rupture of cerebral vessels with the subsequent bleeding. It is worth noting that vasculopathy rarely occurs as a consequence of radiation therapy. Only in two studies out of 7, on the basis of which a review of Bradley et al. was performed, vasculopathy was reported as a consequence of radiotherapy (Bradley et al. 2014). In the study of Luu et al. 16 patients who have treated craniopharyngioma with radiation therapy, only two developed vasculopathy which did not lead to death (Luu et al. 2006). Also in the study of Bishop et al. only two of 19 patients developed vasculopathy, which was not fatal (Bishop et al. 2013). Thus, death from vasculopathy was not reported in any case. Nevertheless, in the proposed study we report the vasculopathy is considered the primary cause of death, since subarachnoidal bleeding is a consequence of vasculopathy, and was caused by an additional pathology, hypertension, related to an increased risk of subarachnoidal bleeding (Feigin et al. 2005). Subarachnial bleeding, in turn, caused secondary consequences, such as pressure on the surrounding brain structures responsible for the basic functions of the body, which was the ultimate cause of death.

Discussion
Craniopharyngioma is a tumor in the pituitary region with an incidence rate of 1.34 in all ages per 1 million (Nielsen et al. 2011). It represents approximately 2.5 – 3% of brain tumors in adults in the United States (Bunin et al. 1998; Karavitaki et al. 2006). Notwithstanding it is histologically benign, its infiltrative behavior affects the pituitary axis, the visual pathways, and other relevant vascular and neural structures and often has a long-term effects sequelae after surgical removal, that obstructs total removal of disease. Optimal therapeutic management of craniopharyngioma continues to be debated (Pietro Mortini et al. 2011). There are no commonly accepted guidelines or a clear consensus for best treatment’s type of craniopharyngiomas in adults, although in some reports published have recommended radiation therapy after subtotal or partial removal of craniopharyngiomas, at least for adults (De Vile et al. 1996; Duff et al. 2000). Nonetheless, optimal treatment’s type should always be determined considering, for example, the patient’s symptoms, age, tumor localization, and extension. Since the discovery of the effects of radiotherapy on cranial tumors, many investigations have been conducted with the patient's observation after treatment and possible outcomes, such as a vasculopathy. The syndrome of radiation-induced intracranial vasculopathy is accepted in the community of radio oncology. Vasculopathy is frequently not comprised of informed consents as a complication of radiotherapy to the brain for pediatric and young adult patients.
The first cases, published in the international bibliography, were reported in 1967 by Darmody et al. (Darmody et al. 1967) after brain irradiation for pituitary adenoma and Lee and Hodes (Lee and Hodes 1967) in consequence of irradiation for optic glioma. Ishibashi et al. reported a case of a 64-year-old woman, who had a chromophobe pituitary adenoma removed and followed by radiotherapy, six years after treatment she developed vasculopathy (Ishibashi et al. 1982). Turel et al., who evaluated retrospectively 42 adults’ patients of which 34 had undergone radiation therapy, reported vasculopathy in one case with worsening of vision, as evidenced by MRI (Turel et al. 2016). Sawamura et al. reported vasculopathy of large intracranial arteries in 3 of 111 patients after irradiation over the parasellar region; two-thirds of these patients had a stroke, 2 and 14 years after irradiation, and one-third developed a huge dural arteriovenous malformation 11 years after (Sawamura et al. 1998).

Although there are many clinical cases of radiation-induced vasculopathy in the published literature, only a small part of them refers to the description of adult patients. The causes of vasculopathy can be implicated with various types of radiation such as Gamma Knife, colloidal gold intracystic instillation, fractionated external beam radiation therapy, and stereotactic radiosurgery. Moreover, it is obvious that any part of the brain may be exposed to the risk of developing vasculopathy. The time interval from the moment of radiation therapy until the onset of symptoms of vasculopathy ranges from 2 to 25 years. But in most cases, vasculopathy is manifested in the first 10 years (Aoki et al. 2002). Notwithstanding this disease has a long latency period, the symptoms that manifest themselves are frequently acute. The course of the disease may have periodic improvements, but in general, it has a deteriorating pattern. Patients in many cases present stroke-like symptoms (Peñagarícano et al. 2004). Increased development of vasculopathy leads to systemic disorders that may involve motor impairment, sensory loss, ataxia, speech difficulty, or decreased cognitive ability. Due to the constantly recurring ischemic episodes caused by vasculopathy, there is a gradual deterioration in the functional status of patients.

In patients with vasculopathy, transdural collateral vascularization may be the main source of blood supply to the part of the brain where there is no damage to the brain vessels. So it is crucial to preserve this vascular anastomosis during the operation. Magnetic resonance imaging of patients suffering from vasculopathy, prior to the use of radiation therapy, can help in determining the sites of stenosis and obstruction in the blood vessels of the brain. The MRI pattern seen after the use of radiation therapy is similar to that expressed in vascular atherosclerosis. Thickening of the endothelium of the vascular walls of the brain can be observed on MRI and several years after the occurrence of occlusion or stenosis. In our case, the patient was treated only with radiation therapy. By dint of multimodal planning of radiotherapy with visual control, it is crucial to exclude large arteries of the brain that do not need treatment and can be injured. In contrast, MR studies and MR angiography can clearly define the boundaries of large arteries. Thus far, there are no proven methods that can reduce the possibility of vasculopathy after radiotherapy. The adjustment of time-dose-fractionation and volume
does not allow to avoid the occurrence of this complication. The administration of corticosteroids prior to and throughout the course of radiation therapy was proposed as a possible prevention option, but its effectiveness remains unproven. It has been reported that baby aspirin treatment is beneficial and may reverse some of the symptoms. Prevention by delaying radiation therapy in young patients for as long as possible remains the best method of treatment. If treatment still needs to be done, then to prevent radiation-induced vasculopathy, modern planning and delivery techniques with conformal coverage and conformal avoidance can be used as the preventive method.

**References**


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