

Blood Brain Barrier Effect Eliminated by Omentum for the Treatment of Glioblastoma Multiforme (WHO IV)

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Abstract

Background: The treatment of Glioblastoma Multiforme (WHO-IV) has not improved over the past century. It is now believed that there may be a way to improve the survival statistics of this lethal tumor.

Methods: It has been shown that placing an intact vascularized omental pedicle on the brain allows omental arteries originating from the omentum to penetrate directly and deeply into the brain. This should allow chemotherapeutic agents flowing through the omental vessels to come in contact with malignant cells of a glioblastoma which are known to be distant from the primary glioma.

Results: In a small experimental study, it was shown that when India ink was injected intravenously in the presence of an omentum on the brain of an experimental animal, the India ink was seen to flow into the depth of the brain, a condition that would be expected if chemotherapy had been present in omental vessels.

Conclusion: This paper will show that it is now possible to bypass blood brain barrier vessels by omental vessels in which chemotherapy would be expected to flow easily into the distal brain and make contact with the malignant cells in brain tissue far distant from the primary glioma.

Keywords: *Glioblastoma Multiforme (WHO IV); Omentum; Blood Brain Barrier Vessels*

Most physicians are aware of the extremely poor survival statistics of patients who develop a glioblastoma multiforme (WHO IV). Despite current treatment of the tumor by surgical excision, radiation therapy, and administration of chemotherapy, it is routinely expected that twelve to fifteen months will occur between the diagnosis of this lethal tumor and the death of the patient. The National Brain Tumor Society states that survival statistics of these tumors is 5.2%. The American Brain Tumor Association reported that 13,390 cases occurred in 2017, and the American Cancer Society claimed that in the 55 - 64 age group, the age that most glioblastoma multiforme (gliomas) develop, only 6% of this group will be alive at five years.

Harvey Cushing, the father of neurosurgery, treated gliomas during his neurosurgical career (1899 - 1933). Unfortunately, the Cushing-Whitney Medical Library at Yale University stated that "Cushing's patient records and surgical records are scattered between Hopkins or Robert (sic) Peter Bent Brigham Hospital where they are missing". It is assumed that Dr. Cushing's survival statistics of gliomas were probably lower than current survival statistics due to less efficient operative and post-operative care at that time. Nevertheless, there has been little improvement in the survival statistics of gliomas (WHO IV) during the past century.

Current treatments for a glioma

Neurosurgery: In excising a glioma the neurosurgeon makes every effort to remove all gross tumor. There does not presently appear to be surgical techniques that would increase patients' survival rates following the excision of a primary glioma (WHO IV).

Radiation: Following complete or incomplete removal of a glioma by surgical excision, the patient is usually referred to a radiation oncologist for routine treatment of the tumor bed and surrounding brain areas by radiation at 60 GY in 30 treatments. Some patients may receive additional radiation techniques that introduce multiple, direct beams of radiation to a specific area of the brain. Although radiation techniques may increase and improve, the fact remains that an increase in radiation can be harmful to brain tissue.

Chemotherapy: If the poor survival statistics of gliomas can be improved, it may likely result from the use of chemotherapy. Treatment would require the introduction into the brain of significant amounts of non-toxic chemotherapeutic substances that could destroy the malignant brain cells that remain in brain tissue following the surgical excision and radiation application to the primary glioma. The chemotherapy that is administered currently, whether by mouth or by intravenous introduction, has limited effect due to the difficulty of chemotherapeutic agents to gain entrance into the brain through the blood brain barrier (BBB) vessels. This paper will report that BBB vessels can be bypassed by omental blood vessels which will allow chemotherapeutic agents to easily infiltrate the brain of patients with a glioma.

Case History

As a young surgeon at Memorial Sloan-Kettering Hospital in New York City, I observed that lymphedema of the arm developed in some women who had undergone surgery and radiation for breast cancer [1]. The idea arose that perhaps the omentum with its vast absorptivity could drain fluid from a lymphedematous arm. Since placement of the omentum into the involved extremity would require surgery, much time was spent in the autopsy room carefully learning the anatomy of the omentum. It became apparent that although massive amounts of atherosclerosis were present in the major arteries of elderly patients, there was a complete absence of cellular material in the lumen of omental blood vessels. The lumens in the omental vessels were completely clear. This finding was published in 1990 in the *Lancet* in an article titled "Lack of Atherosclerosis in Blood Vessels in the Omentum" [2].

A second personal experience that led to the consideration that the omentum might play a role in the treatment of gliomas was based on a discussion with Dr. Patrick J Kelly, the internationally renowned neurosurgeon and Chairman of the Department of Neurosurgery at New York University Medical School. He related that when he was a neurosurgeon at the Mayo Clinic in Rochester, Minnesota, he had surgically resected under computer control 300 gliomas, and after each procedure he biopsied various areas of the brain and in every instance found malignant cells in brain tissue distant from the excised primary glioma. Dr. Kelly's observation explains why, after complete excision of a primary glioma, malignant cells that remain in surrounding brain tissue appear to be the cause of the rapid glioma recurrence that results in the subsequent death of the patient.

The challenge in improving the treatment of a glioma is to find a way in which chemotherapy can easily enter the brain and contact the malignant cells present throughout the brain tissue. BBB capillaries are distinct from normal capillaries in that they have tightly packed endothelial cells in their lumen that act as a barrier to toxic and unwanted substances from penetrating through the BBB capillary wall and entering the brain. If large amounts of effective chemotherapeutic agents could enter the brain over an extended period, BBB vessels would have to be either destroyed or bypassed. Unfortunately, attempts to improve survival statistics in gliomas by either of these methods have failed [3-5]. Eliminating the function of BBB vessels may prove to be extremely difficult or, more likely, impossible to accomplish. However, bypassing BBB vessels by omental capillaries, can be achieved.

If survival statistics for gliomas are to improve, three requirements appear to be necessary. The first is that pharmaceutical companies must develop chemotherapeutic agents of sufficient strength that can destroy malignant brain cells without damaging surrounding brain tissue. The second requirement is that a free flow of chemotherapeutic agents must have the unrestrained ability to enter the brain, a process that does not occur in BBB vessels. The third requirement is that chemotherapeutic agents must be able to contact the malignant cells that are distant from the excision site of the primary glioma. It is these distant malignant cells in brain tissue that Professor Kelly claimed were responsible for the recurrence of a glioma that occurs shortly after the excision of the primary glioma and causes the death of a patient. If these requirements can be accomplished, survival statistics of gliomas could be expected to improve.

Placement of an intact vascularized omental pedicle on the brain of animals [6,7] and humans [8-17] has been shown to allow large amounts of blood to flow directly and deeply into the brain through omental vessels [14]. It seems reasonable to believe that if chemotherapeutic drugs were present in the flowing blood stream in an omental capillary, they would encounter and hopefully destroy malignant cells in brain tissue that are distant from a primary glioma. Such reactions could be expected to improve survival statistics.

Solution

It was learned in the experimental laboratory and later in humans that when the omentum is placed directly on the brain, capillaries originating from the omentum penetrate directly and deeply into the underlying brain. The resultant blood stream flowing through omental capillaries could deliver chemotherapeutic agents throughout the brain, which would allow the contact of chemotherapeutic agents with malignant brain cells. The blood brain barrier vessels would be completely bypassed. A simple experiment listed below can demonstrate this possibility.

As clearly seen in figure 1, when the omentum was placed on the brain of a monkey and India ink injected intravenously, the dye quickly appears in the omentum and is observed flowing through omental capillaries into the distal brain. If chemotherapeutic agents were present in an omental capillary rather than India ink, the chemotherapeutic material would be expected to come in contact with malignant cells present in brain tissue. BBB vessels would be completely bypassed by this activity.

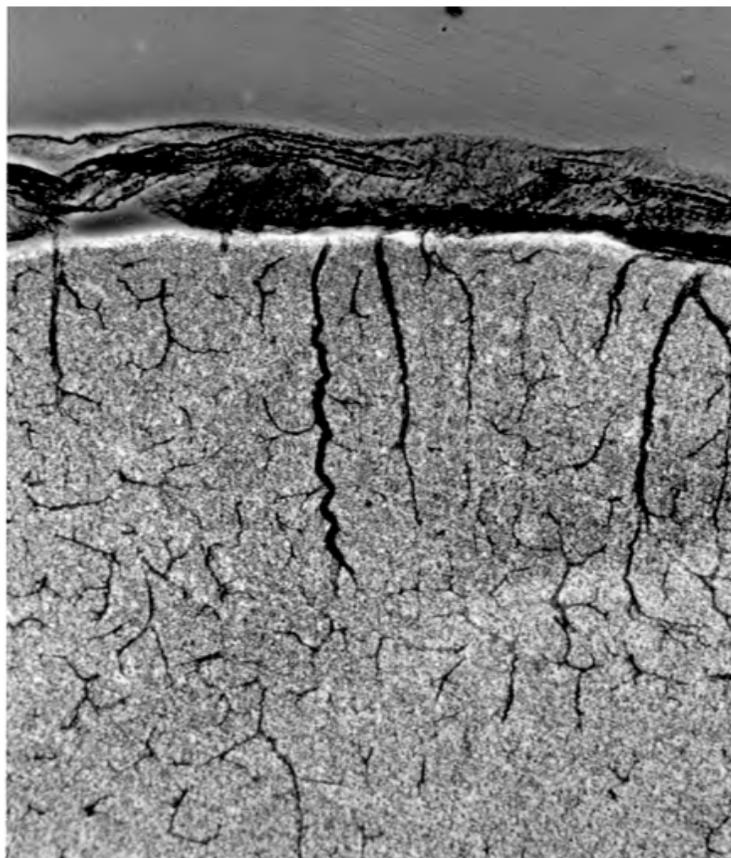


Figure 1: India Ink given intravenously shows the dye in the omentum located on a monkey brain. Note the omental blood vessels delivering blood and India Ink into the depth of the underlying brain. It is expected that chemotherapeutic agents will also have the ability, when present in omental capillary blood flow, to deliver drugs to malignant cells distant from a primary glioma. Blood brain barrier vessels will not be necessary in the process.

Conclusion

Because of the continuing poor results following current treatment of gliomas, omental transposition onto a brain seems worthy of trial. There has not been substantial improvement in the treatment of gliomas (WHO IV) over the past century. It appears that there is much to gain and little to lose by testing the possible beneficial effect that the omentum might have in improving the treatment of gliomas. A rapid evaluation of the omental procedure appears indicated.

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Compliance with Ethical Standards

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Conflict of Interest

Author has received no grants and has no conflict of interest.

Ethical Approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This article does not contain any studies with human participants performed by any of the authors.

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