International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Cytotoxic Titania (TiO_2) Ultra-nanoparticles Functionalized with 1% Platinum for the Treatment of Glioblastoma

Tessy López-Goerne[1-2*], Dulce Gurgua[1]

[1]Department of Health Care, Autonomous Metropolitan University—Xochimilco, Mexico City, Mexico

[2]Department of Nanotechnology, School of Science and Engineering, Tulane University, New Orleans, Louisiana, USA

Citation: Tessy López-Goerne, Dulce Gurgua. Cytotoxic Titania (TiO2) Ultra-nanoparticles Functionalized with 1% Platinum for the Treatment of Glioblastoma. Int Clinc Med Case Rep Jour. 2026;5(11):1-9.

Received Date: 07 November 2026; **Accepted Date:** 10 November 2026; **Published Date:** 13 November 2026

***Corresponding author:** Tessy María López Goerne, Department of Health Care, Autonomous Metropolitan University—Xochimilco, Mexico City, Mexico

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ABSTRACT

This paper presents the clinical case of a patient with glioblastoma (GB)—the most extensively studied tumor in research laboratories because of its high malignancy and its unique ability to sustain itself by taking up nutrients, effectively granting it a "life of its own." Although the tumor is surgically removed and treated with radiotherapy and chemotherapy, it typically regrows rapidly by drawing sustenance from the cerebrospinal fluid (CSF). It actively recruits a wide array of substances, including lipids, lipid droplets, carbohydrates, peptides, and even genetic material. Furthermore, the tumor exhibits resistance to chemotherapeutic agents such as temozolomide or carboplatin, while these drugs simultaneously cause severe neurological side effects in the patient. In this study, we treat the patient's GB using a state-of-the-art Pt/TiO2 nanobiocatalyst that enters malignant cells via receptor-mediated endocytosis without affecting healthy cells. The mechanism of action of these nanoparticles is clearly explained. While traditional GB treatments typically yield a survival period of 6 to 12 months, this innovative alternative offers an average survival of 36 months. Various nanoparticles are currently under investigation to combat this type of brain cancer, and all such alternatives represent a significant improvement over conventional chemotherapy.

Keywords: GB; Ultra-nanoparticles; Pt/TiO_2 (1%) bionanocatalyst; Side effects; Survival

INTRODUCTION

Glioblastoma (GB) is a primary neoplasm of the central nervous system characterized by its highly aggressive nature, infiltrative growth, and high molecular heterogeneity. According to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System, the term "glioblastoma" is reserved for diffuse, adult-type tumors that are IDH-wildtype and exhibit specific histopathological and molecular features—such as necrosis, microvascular proliferation, EGFR amplification, TERT promoter mutation, or a combination of chromosome 7 gain and chromosome 10 loss—thereby enabling a more precise diagnosis [1-3].

The high aggressiveness of glioblastoma is linked to its ability to infiltrate surrounding brain tissue, its significant cellular heterogeneity, and molecular alterations that promote tumor cell proliferation and survival.

Furthermore, the tumor microenvironment plays a crucial role in disease progression through interactions among neoplastic cells, vascular components, immune cells, and the extracellular matrix. These characteristics hinder the complete removal of tumor tissue and facilitate recurrence, even after treatment.

Glioblastoma progression is associated with metabolic reprogramming, characterized by modifications in bioenergetic pathways that favor cell proliferation and survival. Key alterations include increased aerobic glycolysis (the Warburg effect), which promotes lactate production and provides intermediates for biomolecule synthesis. Additionally, glutaminolysis and altered lipid metabolism help maintain mitochondrial function and generate precursors essential for tumor growth. These alterations, along with hypoxia and tumor microenvironment heterogeneity, promote metabolic plasticity, allowing tumor cells to switch between glycolysis and oxidative phosphorylation, which contributes to adaptation and therapeutic resistance [2,3]. Conventional treatment for glioblastoma involves maximal surgical resection, followed by radiotherapy combined with temozolomide, and subsequent cycles of chemotherapy using this alkylating agent. However, despite this approach, tumor recurrence remains frequent, and the prognosis for patients continues to be poor. A primary therapeutic limitation is the difficulty of achieving pharmacologically effective concentrations of antineoplastic agents within brain tissue. In this context, the Blood-Brain Barrier (BBB)—composed of endothelial cells linked by tight junction complexes and associated with other components of the neurovascular unit—regulates the passage of substances from the systemic circulation into the brain parenchyma. Although its integrity may be compromised in certain tumor regions, infiltrative zones may retain components.

CLINICAL HISTORY

Patient EG, 40 years old, presented to the emergency department of the National Institute of Neurology and Neurosurgery with a 4-month history of migraines and headaches. These symptoms were accompanied by nausea, forgetfulness, and reduced attention. Patient EG subsequently developed hypoesthesia on the right side of the body, aphasia, and amnesia. Magnetic Resonance Imaging (MRI) revealed a glioblastoma located in the left temporal lobe, with distortion of the cortical sulci—a finding characteristic of a grade IV intra-axial neoplasm. A biopsy was performed, and histopathological analysis revealed a proliferation of atypical glial cells that tested positive for GFAP. Treatment was initiated with temozolomide (TMZ) in 5-day cycles followed by 28-day rest periods; this was supplemented with intravenous bevacizumab (10 mg/kg) to reduce tumor size. Subsequently, surgery was performed to resect as much of the tumor as possible. Given the highly infiltrative nature of this tumor, an experimental approach was employed during the procedure: a bionanocatalyst consisting of 1% platinum integrated into a titanium dioxide (TiO_2) network, characterized by a nanoparticulate structure with a particle size of 1–3 nm. The patient's family signed an informed consent form, as the patient was receiving palliative care. Three days later, he began radiotherapy and chemotherapy, continuing with the same medications: TMZ and bevacizumab.

MATERIALS AND METHODS

We synthesized the Pt/TiO_2 (NPt) nanomaterial using the sol-gel method, following the standardized parameters described in patent WO 2019/017723 A2. Titanium butoxide (Sigma-Aldrich, 97%) was used as the precursor for the titanium dioxide (TiO_2) matrix, and acetylacetone (Sigma-Aldrich, 99%) as the solvent. Acetylacetonate (Sigma-Aldrich) was dissolved in the reaction mixture until a final platinum concentration of 1 mol% was

reached. Furthermore, to enhance selectivity, functionalizing agents were added to create an analogy with cells. Finally, the resulting gel was vacuum-dried to obtain dry nanoparticles.

The patient underwent surgery for the first time, with the placement of 1 g of nanoparticles. A year later, because the GB tumor had grown back, the patient underwent surgery once again to impregnate the tumor with 2 g of nanoparticles.

RESULTS

Histology

A sample of the patient's tumor was sent to the histology laboratory, where glioblastoma cells were identified, accompanied by a pronounced chronic inflammatory infiltrate (lymphocytes, plasma cells, and a predominance of hemosiderophages). A small cluster of cells with abundant cytoplasm and large, pleomorphic nuclei—suggestive of a neoplasm—was also observed (Figure 1, left). (Figure 1 right) shows glioblastoma (GB) tumor cells following 6 months of treatment with Pt-TiO_2; notably, there is a reduction in both the number and overall quantity of neoplastic cells.

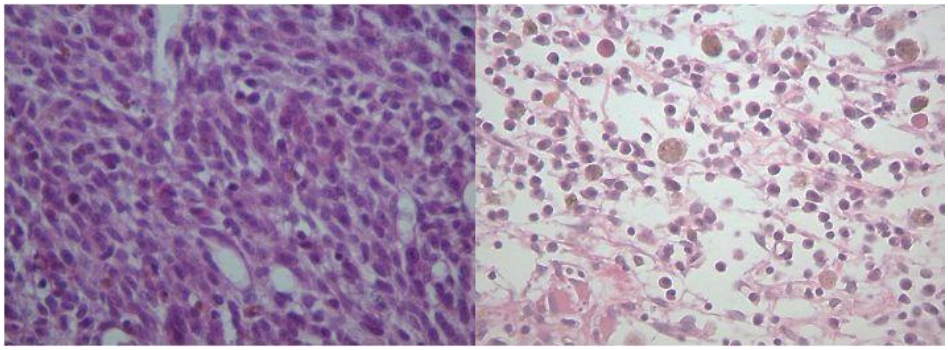


Figure 1: H&E-stained histology of the tumor sample.

MAGNETIC RESONANCE IMAGING (MRI)

An extensive abnormality is observed, primarily within the left cerebral hemisphere and involving deep periventricular regions. The lesion is heterogeneous, with areas of increased signal intensity and hypointense components. The abnormal signal surrounding the affected area is consistent with vasogenic edema or tumor infiltration; there is also evidence of ventricular involvement and possible displacement of adjacent structures. Significant alterations are visible on T2/FLAIR sequences [6].

Post-surgical MRI scans reveal a hypointense region corresponding to the resection cavity, filled with cerebrospinal fluid, alongside anatomical changes from prior interventions. There may also be necrotic components linked to tumor progression, previous radiotherapy, and chemotherapy; clear evidence of edema and inflammation is present (T1-weighted image) [7,8].

Platinum nanoparticles supported on titanium dioxide represent a novel experimental strategy known as "catalytic nanomedicine." In early clinical trials, this approach has yielded better outcomes than conventional treatment. The activity of these nanoparticles varies based on their composition, surface characteristics, oxidation state, and biological environment. They participate in redox reactions and modulate cellular processes associated with oxidative stress [9–11]. Clinical significance of survival. In patients with glioblastoma (GB), median survival with conventional treatment ranges from 12 to 18 months from diagnosis and varies

considerably with age, functional status, and extent of surgical resection [12]. However, when Pt-TiO_2 nanoparticles are used—though the specific follow-up timeline is not fully defined—the average survival reaches 36 months, even without accounting for the exact time of treatment initiation, tumor progression, or other prognostic factors [13].

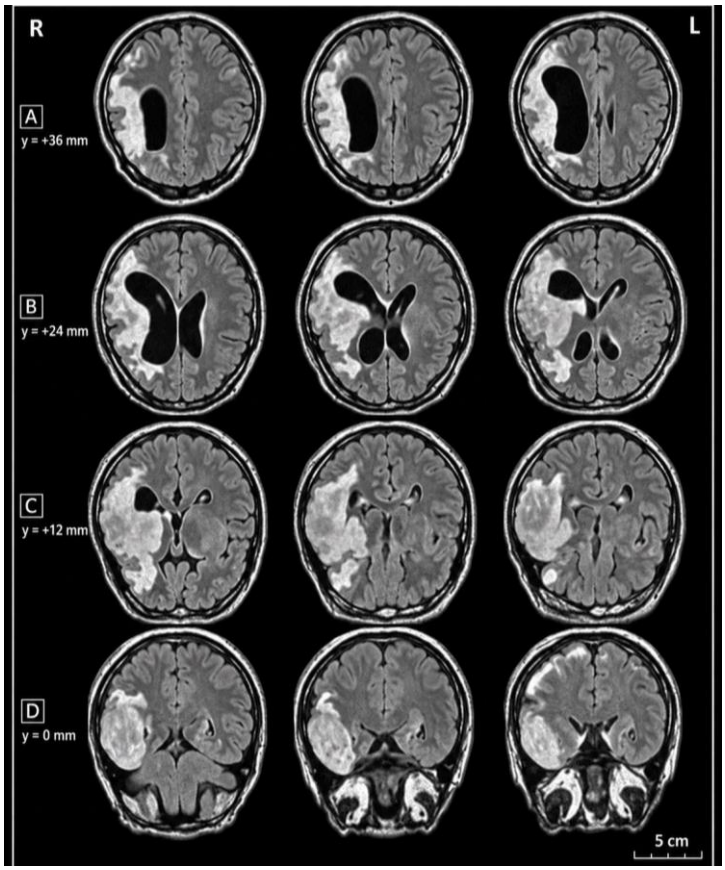


Figure 2: Magnetic resonance imaging (MRI). Brain MRI, coronal view.

OPEN-FIELD SURGERY

Sample preparation.

The Pt nanoparticles (NPt) consist of a very fine, light-yellow powder. They are sterilized before being brought into the operating room, where they are prepared within the sterile surgical field. Figure 3A shows the powder, to which 2 mL of an injectable liquid is gradually added. As shown in Figure 3B, mixing the powder with the liquid creates an intensely yellow dispersion; this is thoroughly blended to form a suspension—depicted in Figure 3C—which is then applied to the GB tumor bed. These nanoparticles, 500 times smaller than a tumor cell, act like projectiles, targeting malignant cells while sparing healthy ones; they disrupt mitochondrial DNA and the nitrogenous bases of nuclear DNA [11–14].

The patient was receiving palliative care, and the family was invited to consent to an experimental treatment—a forward-looking approach to managing glioblastoma (GB) through advanced precision medicine. Given the size of the tumor, an open-field surgical procedure was performed; as much of the tumor as possible was resected without compromising the patient's neurological function. Subsequently, the entire tumor bed was infiltrated with nanoparticles, as illustrated in Figure 4 [15]. These nanoparticles selectively target cancer cells, entering via endocytosis; once inside, they break chemical bonds within the mitochondrial DNA and disrupt energy

metabolism. This shifts cellular processes—replacing the Krebs cycle with the Warburg effect—and triggers programmed cell death, or apoptosis. The nanoparticles enter cells by binding to specific receptors with a distinct chemical conformation compared with those on healthy cells; consequently, healthy cells remain unaffected [14]. Figure 4A shows the tumor bed, with the neurosurgeon using a neuronavigation system; Figure 4B depicts nanoparticle infiltration of the tumor bed. Figure 4C shows intratumoral histology performed during surgery, while Figure 4D shows histology performed 6 months post-surgery.

Micrograph 5A reveals regions of heterogeneous contrast, featuring partially overlapping dark domains and areas with a less ordered appearance. Some regions show structural organization consistent with the anatase crystalline phase, as evidenced by distinct crystal planes. In micrograph 5B, periodic, ordered contrast fringes—consistent with the lattice planes of anatase crystalline domains—are more clearly identifiable. Fringes with varying orientations suggest multiple, possibly overlapping, crystalline domains. Both micrographs include white bars in the bottom-right corner representing a 5 nm scale, allowing determination of particle size.

Figure 6 shows clusters of spherical titania (titanium dioxide) nanoparticles; the clusters appear light, while the pores appear darker. At higher microscope resolution, a clearly defined sphere with darkened mesopores becomes visible. This type of microscopy is highly significant for our work, as greater nanoparticle porosity correlates with higher activity within cancer cells.

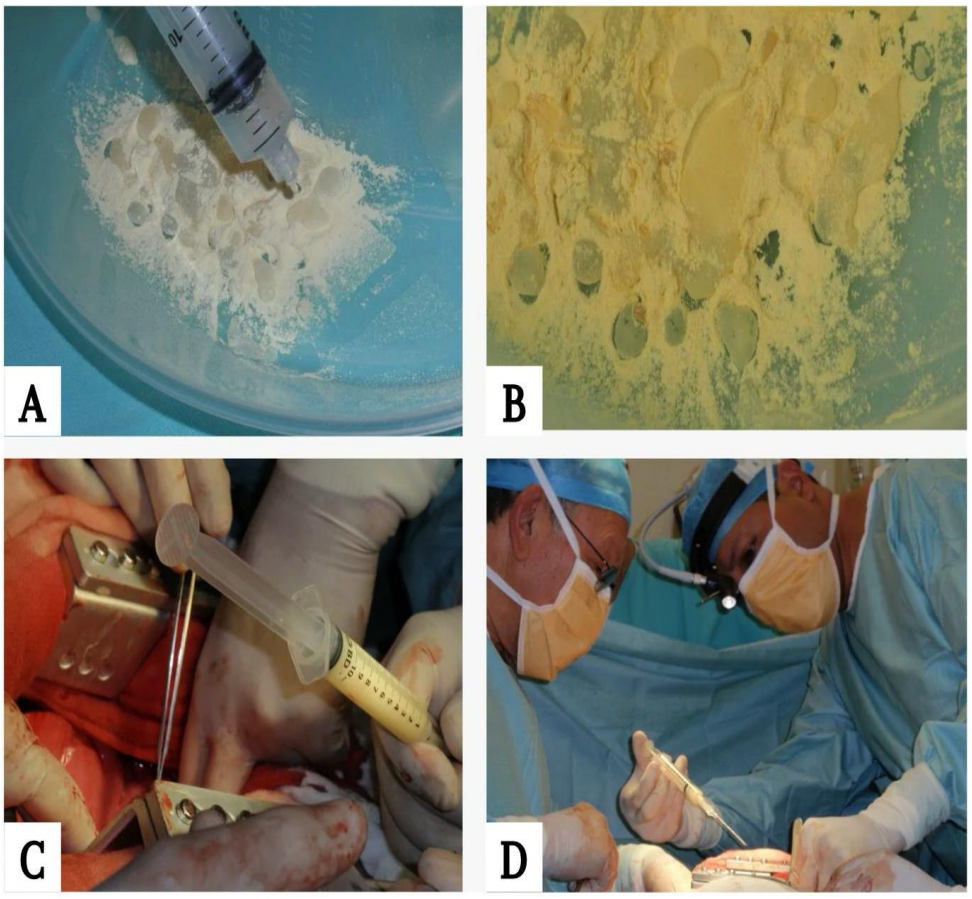


Figure 3: Sample preparation before infiltration into the tumor bed.

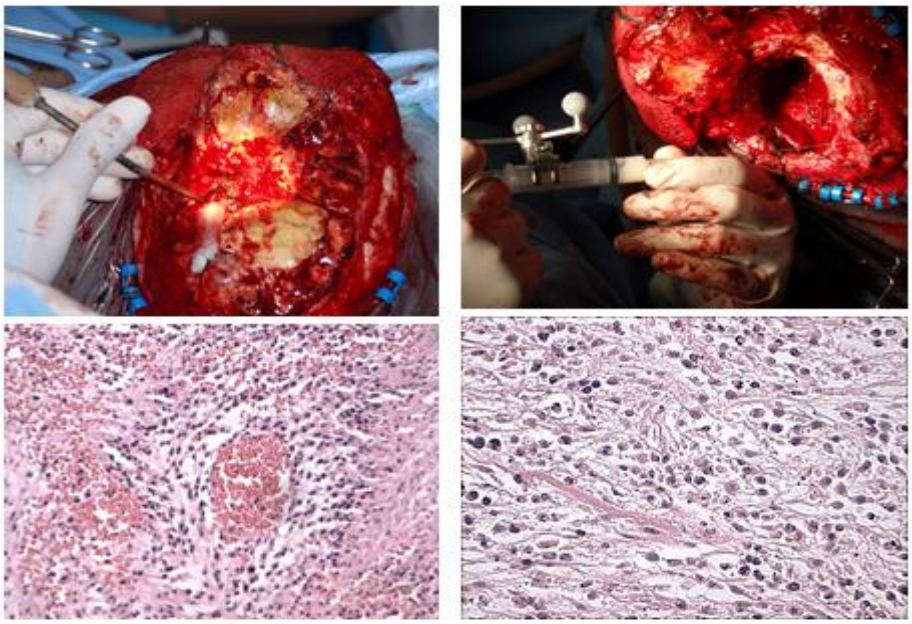


Figure 4: A) Open-field tumor surgery; B) Tumor bed and infiltration with nanoparticles (NPs); C) H&E histology performed during surgery; D) H&E histology 6 months post-surgery [4].

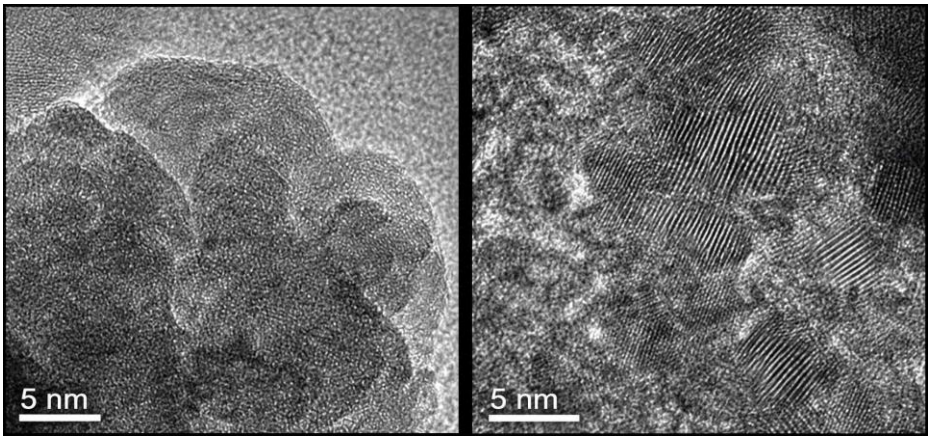


Figure 5: Transmission micrographs.

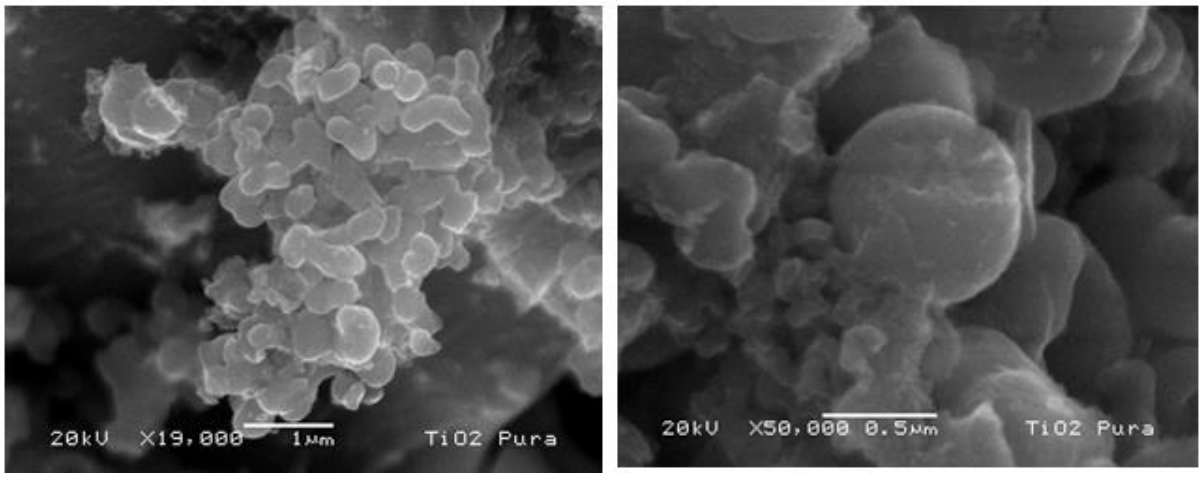


Figure 6: Scanning micrographs.

CONCLUSION

Glioblastoma has been described as the "holy grail" by Beata Pajak, of the Independent Laboratory of Genetics and Molecular Biology, due to the extreme difficulty in combating it. In this clinical case, a patient undergoing compassionate-use therapy was offered a novel treatment: instead of conventional chemical agents or radiation, the tumor was treated with a bionanocatalyst—also referred to as an inorganic "nanoenzyme" with lyase activity. Following open-field surgery, the entire tumor bed was impregnated with Pt/TiO_2 (NPt) containing a 1% platinum concentration. To date, patients who have undergone this procedure have shown an average survival time of 36 months.

Our future research aims to functionalize these NPt particles with specific enzymes and proteins designed to disrupt the Krebs cycle, thereby depriving glioblastoma (GB) of energy and preventing recurrence.

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