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Case Study

Gemistocytic Glioblastoma: A Case Report

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ABSTRACT

Introduction: Glioblastoma Multiforme (GBM) is the most common and lethal malignant primary brain tumor. It is classified by the World Health Organization (WHO) as a group of diffusely infiltrating astrocytoma, representing up to 50% of all primary brain gliomas, and carries the poorest prognosis. Aberrant genetic events and signaling pathways have clearly demonstrated that GBM is highly anaplastic and a morphologically high heterogeneous tumor. ***Method:*** We report a single case of Gemistocytic glioblastomas, in which a 46year male, presented with features of raised intracranial pressure and rapid neurological deterioration. The imaging findings were suggestive of high grade malignancy involving the brain. ***Results:*** This was confirmed as Gemistocytic glioblastoma after surgical excision and histopathological examination. Gemistocytic cells are large astrocytes with plump processes and massive accumulation of glial fibrillary acidic protein (gemistocyte). Their accumulation within astrocytoma may be due to BCL-2-mediated escape from apoptosis. ***Conclusion*****:** In literature, exact incidence of these types of lesions is not known and it needs further evaluation**.** Understanding the genetic alterations, specific molecular biomarker and proliferative pathways may promote therapeutic development for the management of GBM.

Key words: Gemistocytic glioblastomas, Gemistocytes, Astrocytoma, Glioblastoma Multiforme

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INTRODUCTION

Glioblastoma Multiforme (GBM) was introduced by Cushing in second half of nineteenth century and the first surgical intervention on this was conducted in Vienna in 1904. [1] GBM is a primary brain lesion consisting of genetically and phenotypically heterogeneous group of tumors. It is the most aggressive of the gliomas that is collection of tumors arising from glia or their precursors within the central nervous system. The WHO classifies gliomas into four grades, and amongst them most aggressive of all is grade IV or Glioblastoma Multiforme (GBM). Unfortunately, this is the most common of the neural malignancies amongst humans. Ninety percent of glioblastoma Multiforme cases develop de novo (primary glioblastoma) from normal glial cells by multistep tumorigenesis. The other 10 % are cases of secondary neoplasms, developing from low grade tumors (diffuse or anaplastic astrocytoma), which takes about 4 to 5 years. The de novo GBM grows within 3 months. Though genetic and molecular mechanisms underlying development of primary and secondary glioblastoma are different they do not show any morphological difference [2-7]. Cases of glioblastoma have also been reported in infants and children. The involvement of sex hormones and viruses in its oncogenesis have also been suggested. The progress of the tumor is associated with deregulation of checkpoint G1/S of the cell cycle and multiple genetic abnormalities of the tumor cells. Metastasis of these are rarely described. Treatment usually comprises of tumor resection, radiotherapy and chemotherapy drugs inhibiting integrin signaling pathways and immunotherapy have also been employed [4].

CASE REPORT

This 46-year-old male patient presented with progressive on and off dull headache with a history of four months associated with vomiting and blurring of vision for last 15 days. No history of loss of consciousness, convulsions, diabetes, hypertension, tuberculosis, asthma. Patient is chronic alcoholic. On examination the patient was conscious, drowsy, disoriented, afebrile with G.C.S.: - 15/15 and no other focal neurological deficit Neurological examination was normal except bilateral papillo-edema. CT scan showed a contrast enhancing left parieto occipital mass lesion. MRI brain was suggestive of neoplastic etiology- Glioblastoma most likely. The tumor was almost entirely removed surgically. Histopathology of the excised specimen from left parieto occipital lobe showed areas of necrosis, anaplastic, poorly differentiated, pleomorphic astrocytic tumor cells, with marked nuclear atypia and microvascular proliferation. Few foci show fusiform round or pleomorphic cells with epithelial differentiation showing gemistocytes having copious, glassy and non-fibrillary cytoplasm displacing angulated nucleus in the periphery of cell. Extensive areas of necrosis are noted with no inflammatory cells. Some areas showed small irregularly shaped, radially oriented densely packed small fusiform glioma cells in pseudo palisading pattern. Microvascular proliferations are noted, in the necrotic areas. Mitotic activity is high. No giant cell reactions noted in the sections examined. Histopathological examination suggestive of Glioblastoma Multiforme with Gemistocytic proliferation.

DISSCUSSION

Glioblastoma Multiforme is the most aggressive of the gliomas, a collection of tumors arising from glia or their precursors within central nervous system. Clinically, gliomas are divided into four grades and the most aggressive of these, grade 4 or glioblastoma Multiforme (GBM), is also most common in humans. Because most patients with GBMs have mortality of less than a year and essentially none have a long-term survival, hence these tumors have drawn significant attention and likewise they have evaded increasingly cleaver and intricate attempts at therapy over the last half-century. One of the reasons for the resistance of GBM to therapeutic intervention is the complex character of the tumor itself. As the name implies, *glioblastoma is multiforme.* Grossly, showing regions of necrosis and hemorrhage and microscopically, with regions of pseudo palisading necrosis, pleomorphic nuclei and cells and microvascular proliferation and genetically with various deletions, amplifications and point mutations leading to activation of signal transduction pathways downstream to tyrosine kinase receptors such as epidermal growth factor receptor (EGFR) and platelet derived growth factor receptor (PDGFR), as well as to disruption of cell-cycle arrest pathway by JNKα4-ARF loss or by p53 mutations associated with CDK4 amplification or RB loss [8,9]. Necrotic foci are one of the most characteristic features of GBM. Histological presentations of the tumor vary depending on location and size of the necrotic foci depending on which, primary glioblastoma presents with long areas of necrosis within the central area of the tumor, resulting from insufficient blood supply. The other type contains small, irregularly shaped necrotic foci surrounded by pseudo palisading area created by radically oriented oval cells observed in both primary and secondary glioblastomas [15]. These tumors also show intra tumor genetic heterogeneity with sub clones existing within the tumor cell population [16]. It has been estimated

that cultured neoplastic and p53-deficient cells may have mutations in any given gene at a rate as high as 1 in 1,000 cells [17]. If this is approximately correct for GBMs in vivo, then one would expect a tumor of 10^9 cells to harbor as many as 10^9 cells with mutations in any given gene. One of the main reasons that the gliomas are not cured by surgery is the topographically diffuse nature of the disease. In addition to the above-mentioned variability within the tumor proper, the location of the tumor cells within the brain also is variable, resulting in the inability to completely resect this tumor. In 1940, Scherer described the appearance and behavior of glioma cells migrating away from the main tumor mass through the brain parenchyma [18]. The patterns of glioma cell infiltration have since been referred to as the secondary structures of Scherer. These glioma cells migrate through the normal parenchyma collect just below the pia margin (sub pia spread), surround neurons and vessels (peri-neuronal and perivascular satellitosis), and migrate through the white matter tracks (intra fascicular spread). This invasive behavior of the individual cells may correspond to the neoplastic cells reacquisition of primitive migratory behavior during central nervous system development. The ultimate result of this behavior is the spread of individual tumor cells diffusely over long distances and into regions of brain essential for survival of the patient. The extreme example of this behavior is a conditions referred to as gliomatosis cerebri, in which the entire brain is diffusely infiltrated by neoplastic cells with minimal or no central focal area of tumor per se [19].

The etiology of GBM is not fully elucidated, from histopathological point of view, the majority of GBMs are diagnosed as de novo or primary tumors, are more common in males and manifest a very rapid development of clinical symptoms develop from normal glial cells by multistep tumorigenesis. Secondary GBM progresses from lower grade tumors (WHO grade II/III) with a mean progression time approximately 55 months [12]. Secondary GBM is observed in younger patients, is more evenly distributed between the genders, and exhibits longer survival time [13,14] Secondary GBM, may be diagnosed clinically (neuroimaging) or histological evidence of evolution from a less malignant astrocytoma. [15] Familial forms of tumors has been described in 1% of cases [10]. GBM has also been associated with diseases like Tuberous Sclerosis, Turcot Syndrome, Multiple Endocrine Neoplasia Type II A and Neurofibromatosis I. [10,11] Amongst women, the postmenopausal have shown a higher risk of its occurrence so a hypothesis on the involvement of sex hormones in development of glioblastoma was created. [4]

Glioblastoma Multiforme is morphologically highly heterogeneous tumor, with cellular composition showing marked variation even in a single tumor mass resulting in mixed histological presentation [12]. In the current WHO classification three GBM variants are recognized as distinct clinico pathological entities i.e. Conventional GBM, Giant cell GBM and Gliosarcoma.

In the conventional GBM category the cellular composition is variable and heterogeneous and may include fibrillary, Gemistocytic and sometimes giant cells. Franz Nissl first described Gemistocytes as glia (*gemaestete glia*) with voluminous cytoplasm. They contain plump, glassy, eosinophilic GFAP – immuno-reactive cytoplasm; eccentric, irregularly shaped, hyperchromatic nuclear; and short cytoplasmic processes. Once thought to represent a reactive component, these cells have been found to harbor p53 mutations and cytogenetic abnormalities (chromosome 7 p gains and 10q losses) therefore they are now thought to represent a true neoplastic component [13]. Perivascular lymphocytic infiltrates are also a common but non-specific finding in these tumors.

Although gemistocytes may be found in all grades of astrocytoma (II, III & IV), Gemistocytic astrocytoma is currently recognized as a distinct variant only of diffuse astrocytoma (WHO grade II), In this context, the WHO defines a Gemistocytic astrocytoma as an astrocytoma composed of more than 20% gemistocytes. The prognostic impact of Gemistocytic cytology in astrocytoma has been an active area of investigation during the last 40 yrs. Various reports have quantified the percentage of gemistocytes present in tumor, a feature termed the Gemistocytic index and sought to correlate its significance with patient outcomes. Gemistocytic astrocytoma (WHO grade II) and greater than 5% gemistocytes have been reported to progress more rapidly to GBM. Some groups have suggested that these tumors behave more aggressively than their non-Gemistocytic grade II counterparts and thus deserve a grade III designation. However, the prognostic significance of the Gemistocytic index in grade II and III astrocytoma still remain unclear and no studies have examined the independent significance of this factor in tumors with the grade IV features of MVP and or necrosis [14].

The primary diagnostic tool for GBM is magnetic resonance imaging. The tumor diameter at the time of diagnosis is usually approximately 4 cm however contrary to this, in a study conducted by Simpson et.al they showed that in 38% of 645 patients the tumor diameter at the time of diagnosis

was <5cm, in 56% cases was within 5-10 cm while in 6% of patient the tumor was >10% [21]. Confirmatory diagnoses are based on histological examination of the intraoperatively removed tumor or its parts, with traditional histological, histochemical and cytological methods. At times when neurosurgical tumor resection is not possible fine needle aspiration biopsy can be performed [22].

The treatment of glioblastoma remains difficult as no cotemporary treatments are absolutely curative. Multiple challenges remain, including tumor heterogeneity, location as in where the region is beyond reach of local control and rapid and aggressive tumor relapse. Hence the treatment of patients with malignant glioma still is palliative and encompasses surgery, radiotherapy and chemotherapy.

While overall mortality rates remain high due to the poor outcome of the standard treatments for GBM and of the diffuse nature of the disease, recent approaches in understanding molecular mechanisms and gene mutations combined with clinical trials are leading to more promising and tailored theuraptic approaches. A number of lever attempts recently have been made with the aim of killing neoplastic cells far from the tumor proper. These have been designed to entice the immune system to reject the tumor, to transfer lethal genes to the tumor cells with gene therapy, or more recently is the use of viral vectors that replicate in and thereby lytically kill tumor cells. They use viruses that normally infect the CNS and have undergone modification to become nonpathogenic to normal tissues but remain lytic to neoplastic cells [23]. Although the available standard of therapy for GBM has evolved into multimodality measures, the majority of patients still experience tumor progression due to the diffuse infiltration of malignant tumor cells into the brain tissues following this treatment. Thus, new ideas and more sensitive methods for treatment have been proposed to target therapies with the goal of increasing the specific efficacy for these patients [20]. Additionally, radiation has been promoted in the form of stereotactic radio surgery for newly diagnosed GBM or tumor recurrence.

CONCLUSION

GBM is the most common and malignant brain tumor in adults and carries the poorest prognosis. Recent progress in molecular biology, neuroimaging and neurosurgical care, has led to the increasing use of new targeted therapies on a multi-modality standard treatment basis in the management of GBM. The median survival time for patients with GBM has improved from an average of 12 months. The molecular based targeted therapies being tested in clinical trials represent a new era in GBM therapeutics that bring hope to those individuals who are afflicted with this refractory disease, which may have a significant impact on quality of life for patients with GBM.

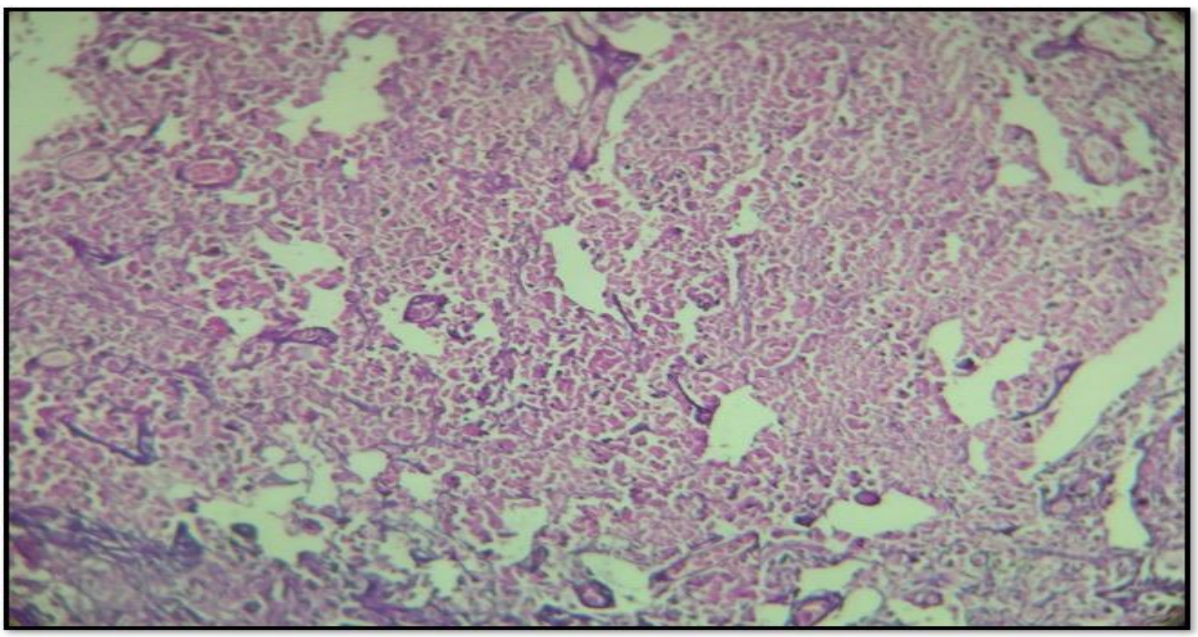

Fig 1: Shows the two morphologic features essential for the diagnosis: necrosis and endothelial proliferation.

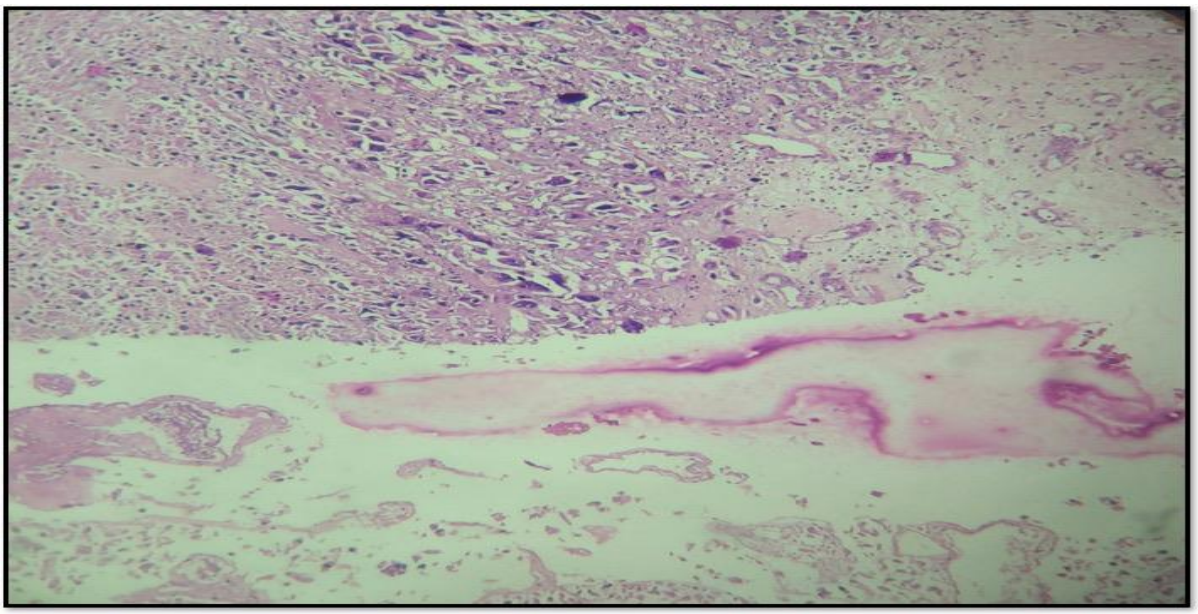

Fig 2: The tumor shows serpiginous necrosis with palisading tumor cells around necrotic foci.

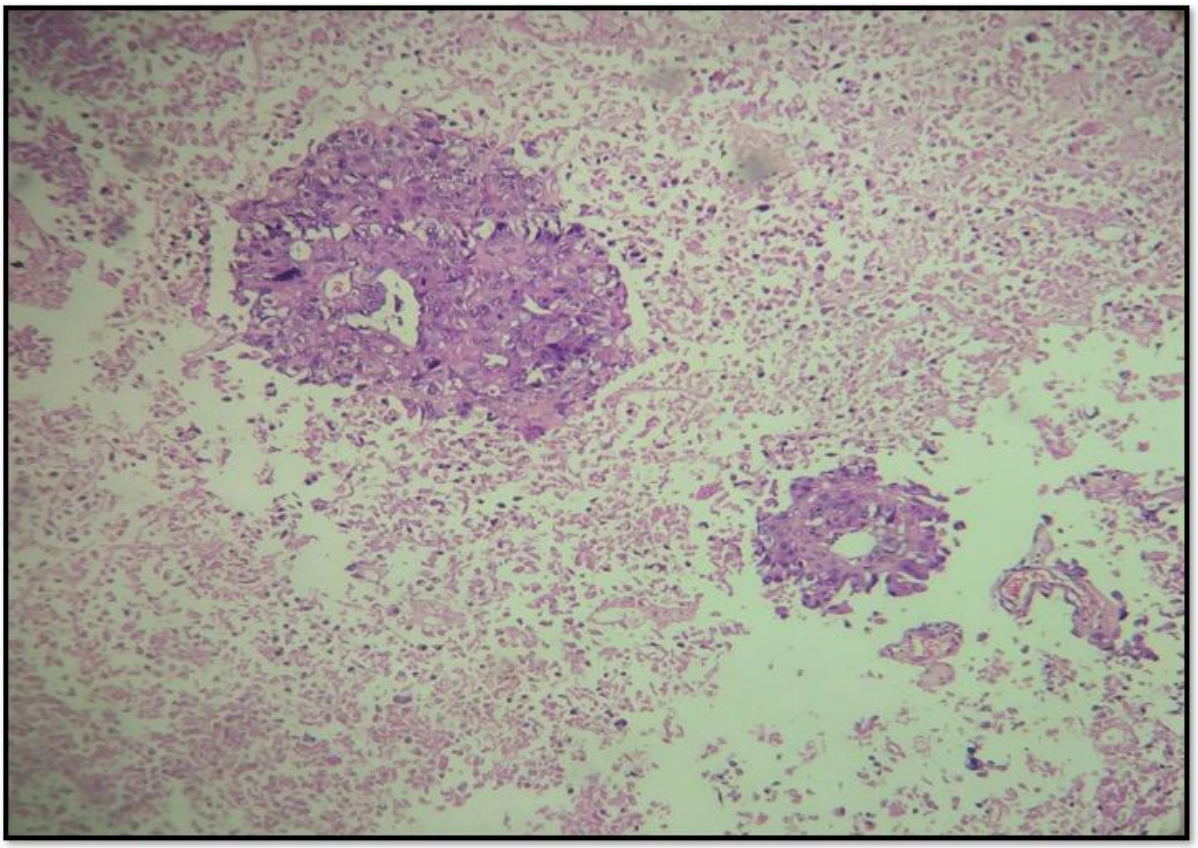

Fig 3: Anaplastic, nuclear atypia, cellular pleomorphism, mitotic activity with necrosis and microvascular proliferation and hypertrophy with formation of multiple lumina resembling glomerulus

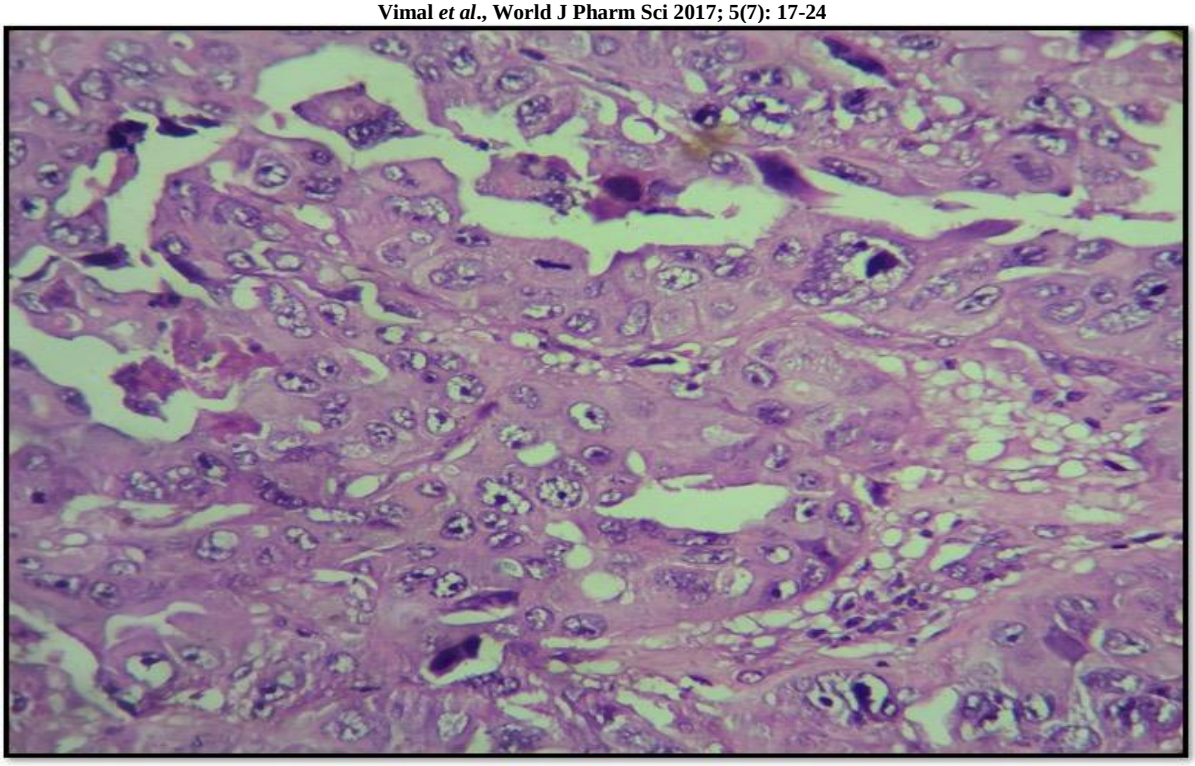

Fig 4: The tumor is hyper cellular and composed of variety of cell types including small cells with hyperchromatic nuclei and frequent mitoses.

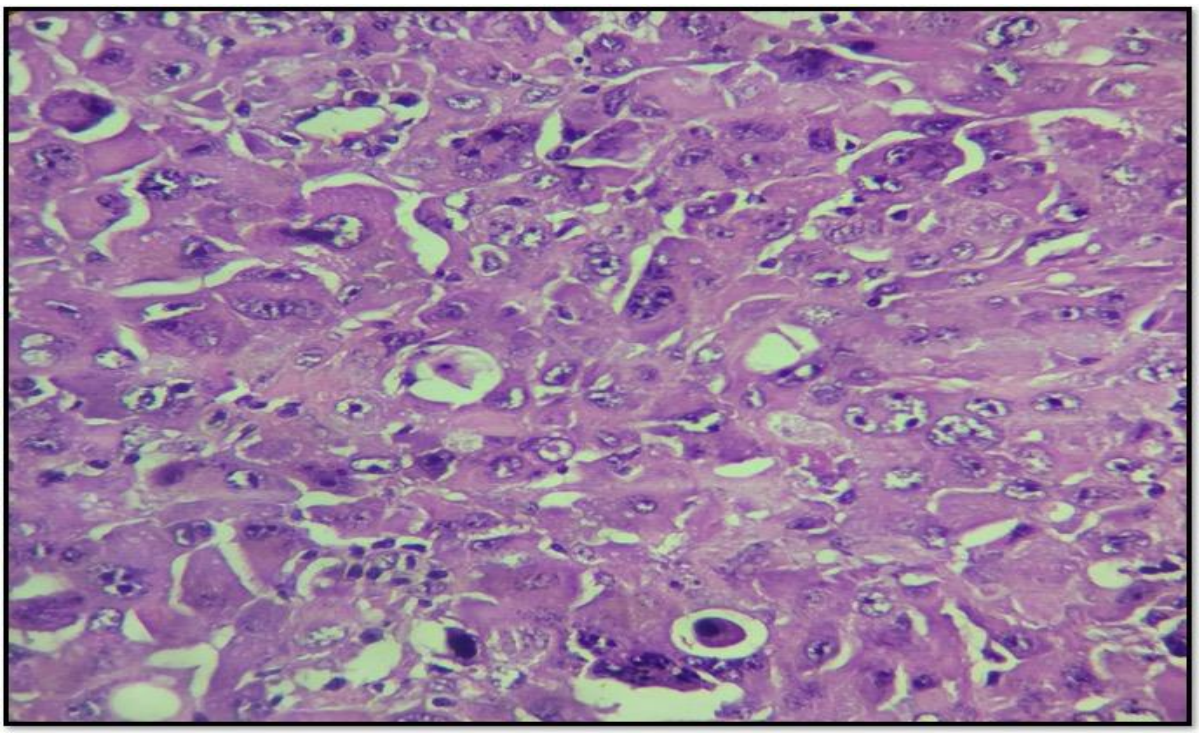

Fig 5: This image shows an area composed of Gemistocytic cells suggestive of evolution from gemistocytic astrocytoma. However, micro gemistocytes can also be seen in an otherwise de novo glioblastoma with no other evidence of a prior glial neoplasm.

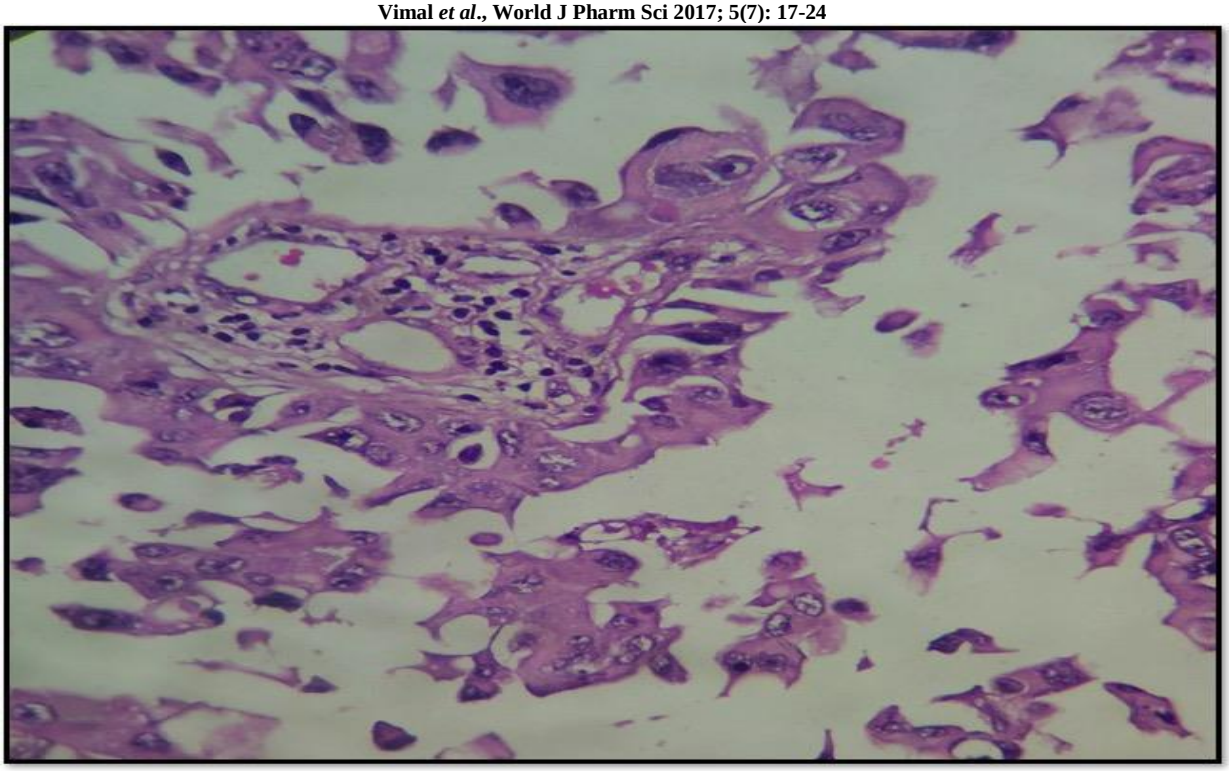

Fig 6: Image showing perivascular lymphocytic infiltrate along with tumor

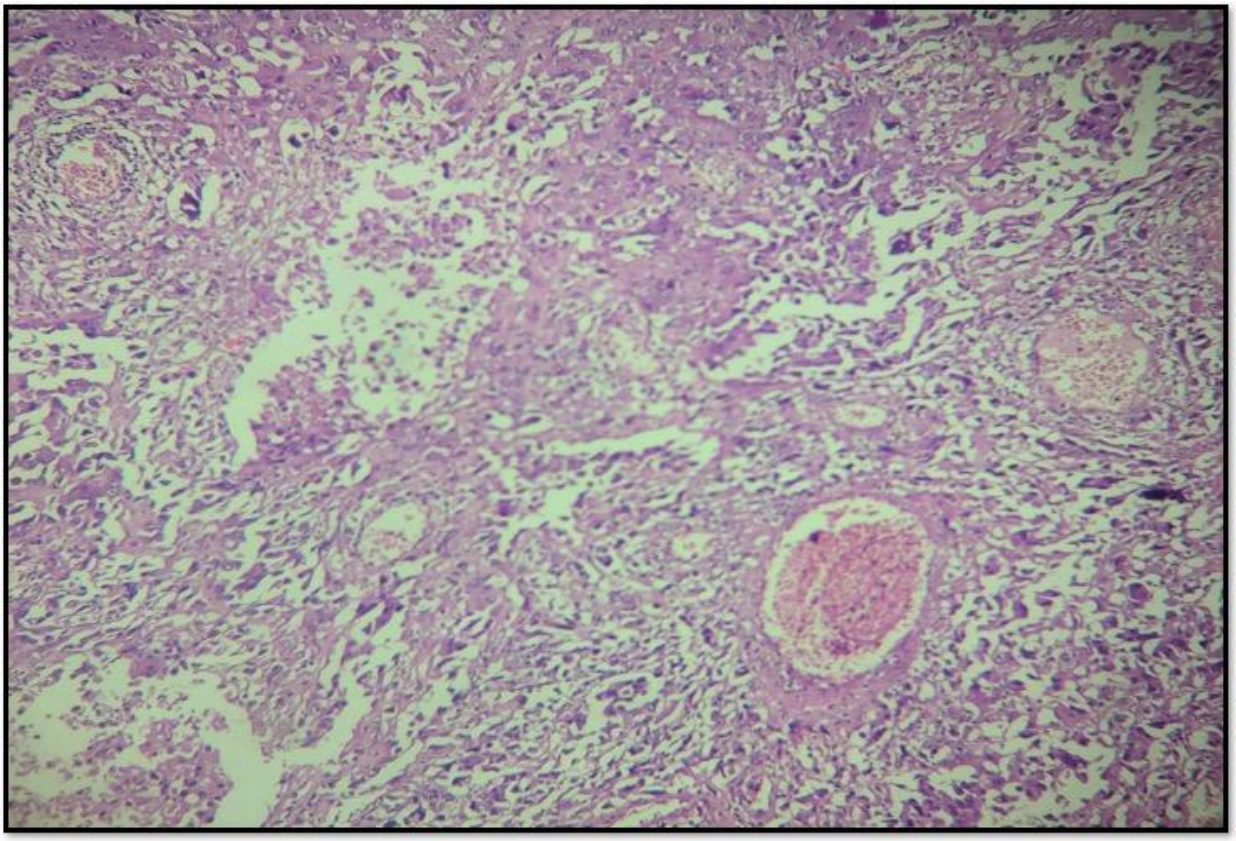

Figure 7: Image shows pseudo palisading necrosis, pleomorphic nuclei and cells and microvascular proliferation

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