A 17-year-old boy presented at our clinic with multiple episodes of loss of contact with the surroundings, olfactory hallucination and seizures in the previous five months. On evaluation, he was found to have a well defined mass in the right middle cranial fossa. MRI of the brain revealed an 8.7 x 5.6 x 6.9 cm mass in the right middle cranial fossa, extending superiorly into the sylvian fissure and minimally into the anterior cranial fossa with predominant extra axial component. It was hyperintense on T2 and FLAIR images with hypointense areas on T1 weighted images. There was evidence of uncal herniation and mild perilesional oedema. Suspecting a high-grade glioma he underwent right fronto-temporal craniotomy and maximal safe resection of the mass. The histopathology was reported as Glioblastoma multiforme (GBM) and he received radiation therapy along with concurrent chemotherapy with Temozolomide. Radiation dose of 50.4 Gy was administered using parallel opposed lateral beams in 28 sittings. The radiation field is shown in the figure. The concurrent dose of Temozolomide given was 100 mg daily and he tolerated the treatment without breaks or major side effects. This was followed with 12 cycles of adjuvant chemotherapy with Temozolomide (cycle 1 - 220 mg [150 mg/m²] and cycles 2 to 12 - 310 mg [200 mg/m²] Days 1-5 repeated every 28 days), which was completed in July 2009, 14 months after diagnosis. At the end of adjuvant therapy, he was evaluated with CT scan of the brain, which showed no evidence of residual disease.

He was on a regular follow up after completion of treatment for next one and a half years when he presented with swelling in the glabellar region for two months, associated with pain, peri-orbital puffiness, occasional epistaxis from the right nostril and nasal blocks and right sided neck swelling. FNAC from the neck node was reported as malignant small round cell tumour. For further characterization, biopsy of the node was done and immunohistochemistry showed pancytokeratin positive, NSE+, CD56+ and synaptophysin negative, CD99- and MYF4-. A diagnosis of metastatic malignant round cell tumour consistent with sinonasal undifferentiated carcinoma or large cell neuroendocrine carcinoma was considered. MRI Brain revealed an extensive lesion in the ethmoids extending intracranially to bilateral frontal lobes and extending to the orbit and lower to the nasal cavity and also a lesion in the pons and multiple neck nodes. There was no recurrent lesion seen at the initial primary site. The lesion in the pons was considered to be a recurrent GBM. Nasopharyngolaryngoscopy showed an ulcerative-proliferative growth in the right nasal region. A biopsy of the growth was reported as undifferentiated sinonasal carcinoma with pancytokeratin positivity. MRI Brain revealed an extensive lesion in the ethmoids extending intracranially to bilateral frontal lobes and extending to the orbit and lower to the nasal cavity and also a lesion in the pons and multiple neck nodes. There was no recurrent lesion seen at the initial primary site. The lesion in the pons was considered to be a recurrent GBM.

Keywords: Long term chemotherapy, Radiation induced cancer, Sinonasal undifferentiated carcinoma
Gliomas are the most common malignant primary brain tumours. They are classified histologically according to WHO grading (I-IV) [1]. The histological subtypes are: astrocytic, oligodendroglial, and oligoastrocytomatic tumours. WHO Grade III and IV are the high grade gliomas which are most malignant and have a bad prognosis. Glioblastoma Multiforme (GBM) is classified as WHO Grade IV and has the most dismal prognosis. However, with the changing treatment over the last decade, the prognosis of GBM has improved [2,3]. There are published reports of patient surviving beyond two years following treatment [4].

**DISCUSSION**

Gliomas are the most common malignant primary brain tumours. They are classified histologically according to WHO grading (I-IV) [1]. The histological subtypes are: astrocytic, oligodendroglial, and oligoastrocytomatic tumours. WHO Grade III and IV are the high grade gliomas which are most malignant and have a bad prognosis. Glioblastoma Multiforme (GBM) is classified as WHO Grade IV and has the most dismal prognosis. However, with the changing treatment over the last decade, the prognosis of GBM has improved [2,3]. There are published reports of patient surviving beyond two years following treatment [4].

**Temozolomide (TMZ)** is an alkylating agent which is used for the treatment of these high grade gliomas concomitantly with radiation therapy and as an adjuvant therapy. The haematological malignancies like myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL) have been described to occur after treatment with TMZ [5-9].

The case presented here is of a 17 year old who was treated with radiation and long duration Temozolomide for a GBM and presented with in two years with a non haematological solid malignancy outside the radiation field.

**Radiation therapy causing second malignancy**

Radiation therapy has been implicated in the causation of second malignancies. Radiation induced meningiomas and gliomas are seen in patients who have received radiation therapy to the brain, head and neck region or scalp [10,11]. The median time duration between radiation therapy and occurrence of second malignancy has been reported as more than five years. The Cahan’s criteria [12,13] for radiation induced malignancy states that for being called a radiation induced second malignancy, the tumour i) should have arisen in the irradiated field, ii) should have a latent period of more than four years between irradiation and induced malignancy, iii) the two tumours must have different histology, iv) induced malignancy should have occurred in a previously normal tissue.

In our patient, scatter doses may have gone to the sinonasal region leading to the causation of an infiel field second malignancy. However, the development of the tumour within two years of radiation therapy may not relate to a radiation induced malignancy as per the above said criteria.

**Temozolomide (TMZ) causing second malignancy**

TMZ is an alkylating agent which gets converted to an active compound, 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC) inside the body for its anti-tumour activity. It interferes with the DNA synthesis which causes cell death. Before TMZ was used for gliomas, several other alkylating agents such as carmustine (BCNU), lomustine (CCNU), and ACNU were being commonly used in the treatment of malignant gliomas. They were known to be strong leukemogenic agents and treatment-related MDS (MDS) or acute leukemia (ALL) with these nitrosoureas were reported [14]. As TMZ is relatively newer agent for treatment of gliomas, its leukemogenic activity has not yet been fully evaluated. Recently few cases reporting MDS/ALL have come up [15], however, most of them had received other alkylating agents along with TMZ. Our patient had not received any other chemotherapeutic agents other than Temozolomide prior to the development of the second malignancy. A longer duration of use of Temozolomide may increase chances of second malignancies, but there is no evidence to suggest that the episode presented may be related to the same.

**SEER data suggesting second malignancy**

SEER database suggests that the second primary cancers are showing an increasing trend with improved treatment modalities leading to better cure rates and longer survival rates of patients [16]. It has thus become an important concern in oncology treatment nowadays. Presently, there is enough evidence of second malignancies resulting after treatment with radiation therapy and chemotherapy.

Sinonasal undifferentiated carcinoma (SNUC) is a rare and highly aggressive tumour of the paranasal sinuses. It carries a poor prognosis. Early case reports have described patients with clinically advanced lesion at initial presentation which were surgically unresectable and survival was in months even after aggressive treatment with chemotherapy and radiation [17-20]. There are no case reports of SNUC presenting as second malignancy.
Metachronous malignancy

Metachronous cancers are multiple primary tumours that develop at different time intervals and are being seen more commonly with improved survival of cancer patients. It has been seen in a recent review that the average interval between the primary cancers and secondary cancers was 6.5 years for men and 4.8 years for women [21]. Patients with colorectal cancer have been commonly found to have metachronous lesions [22]. It has also been described in other malignancies like breast carcinoma and lung carcinoma. There are no reports of metachronous malignancy in GBM. Having reviewed the possibility of being a second malignancy induced by radiation and or Temozolomide, this case fits in as a metachronous cancer until more evidence is unearthed or more associations of SNUC following use of Temozolomide is published in literature.

A remote possibility of the undifferentiated carcinoma being a secondary from an occult primary possibly in Nasopharynx or other sites may also be postulated.

CONCLUSION

Second malignancies are known to occur after treatment with radiation therapy and chemotherapy. However, they are usually seen after 5-10 years of treatment. This patient presented with a second malignancy within a shorter time period and its occurrence was outside of the radiation field, which makes it unlikely to be attributed to radiation-induced cancer. Appearance of solid malignancy after long-term temozolomide is in contrast with earlier reports of hematological malignancies after use of this alkylating agent. Our case probably fits in as a metachronous cancer or a remote possibility of secondary carcinoma from an occult primary, until similar reports of second malignancies post chemotherapy emerge in future.

REFERENCES