



Case Report

Radiotherapy in advanced sino-nasal mucosal malignant melanoma, after progression with temozolomide treatment: A case report with literature review

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Abstract

Background: Nasal mucosal and paranasal sinus melanomas are very rarely seen. These tumours are resistant to therapy and rates of regional recurrence and distant metastasis are very high. Surgery has been the primary treatment modality. Radiotherapy, immunotherapy and chemotherapy are other therapeutical methods.

Case: In our sino-nasal mucosal melanoma (SNMM) case, disease was progressed following temozolomide therapy. Consequently, radiotherapy was initiated to the head and neck region of the patient, with a total dose of 6600 cGy. The control paranasal CT taken after two months revealed that a full response was obtained in the primary tumour.

Discussion: In our case, a full local control was achieved with radiotherapy initiated following the progression after two courses of temozolomide.

Introduction

Malignant melanoma evolves out of neuroectodermal derived melanocytes. The most common location is the head and neck region (25-30%). The second most common locations are the trunk in men and extremities in women. The tumour rarely involves the mucosa. Malignant melanoma can be located in the intestinal and genital systems and nasal, paranasal, nasopharyngeal and leptomeningeal mucosa may also be encountered (1-4%). Those which are located in the nasal cavity and paranasal sinuses are very rare and their outcomes are relatively poor.¹ Nasal mucosal melanoma is a very rare and aggressive progressive melanoma type.¹⁻³ Mucosal melanoma usually presents at a more advanced stage and is therefore associated with a higher mortality rate than cutaneous melanoma

because of its location and rich vascularisation.^{4,5} Also, exposure to sunlight is not an etiologic factor in this type of melanoma. However, irritant compounds in the air such as tobacco smoke have been implicated in the development of head and neck mucosal melanomas. Generally, the first complaint is nasal bleeding and nasal obstruction.³

Craniofacial resection has been recognized as the gold standard for skull base involvement.⁶ Tumour size, lymph node involvement and the response to initial treatment were found to be the most important prognostic factors with multivariate analyzes.⁷ Cisplatin, dacarbazine and vindesine combination is one of the best chemotherapy regimens in patients with metastatic disease. While lymph nodes and brain metastasis achieve good results, the other organs have low response rates with chemotherapy.⁸

Five year survival rates are 10-40% at an early stage,

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and the median survival is 15 months. The best outcomes are achieved with postoperative radiotherapy in operable cases. Survival rates have been increased with the addition of radiotherapy and immunotherapy to surgery.⁹⁻¹² In a meta-analysis, nasal mucosal melanoma had a 31% 5-year survival rate, whereas sinus melanoma patients had a 0%, 5-year survival.¹³ The same meta-analysis showed that 73.1% of patients who had local failure developed distant metastases, whereas those with local control developed distant metastases at a rate of 52.1%.¹³

Five year survival rate was reported to increase as high as 67% in patients with the addition of Lymphokine Activated Killer cell (LAK) treatment.¹⁴ Some studies were conducted with dendritic cell immunotherapy in advanced melanoma. Addition of low dose temozolomide to dendritic cell immunotherapy causes depletion in CD4+CD25++Foxp3+ regulatory T-cell lymphocytes as well as in growth factors, resulting in a more efficient treatment.¹⁵

The effectiveness of chemo-hormonal intra-arterial treatment has not exactly been proven, however some studies show good results.^{16, 17}

Determination of certain changes in the molecular pathogenesis of mucosal melanoma in the future will enable the application of more effective systemic treatment methods.¹⁸

Increase in sMICB (soluble major histocompatibility complex class I, group B) reduce natural killer cell immunization. sMICB rate significantly increases in mucosal melanoma. Appropriate treatment can be selected by testing the sMICB.¹⁹ Over expression of c-KIT, a receptor tyrosine kinase, was reported in 39% to 88% of mucosal melanomas.^{20,21} This mutation was associated with sensitivity to imatinib *in vitro*. c-KIT is a key regulator of mucosal melanoma and proliferation of melanocytes.²² It has been shown to activate the intracellular signalling pathways related to tumour progression.²³ Marked tumour regression was observed in metastatic mucosal melanoma with single-agent imatinib.²⁴ Distant spread in general is associated with rapid clinical deterioration and a short survival time.²⁵

Case Report

Our case is a 54-year-old male patient who was diagnosed with a dental abscess during examinations performed upon complaints of headache, continual nasal bleeding, which increased gradually for about 4 months; his tooth was extracted after antibiotherapy. As the patient experienced a substantial increase in headaches after the extraction of his tooth, MRI was applied. A mass was determined filling the left paranasal sinuses, nasopharynx and involving the skull base. Following biopsy, the pathological outcome was determined as paranasal mucosal malignant melanoma (figure 1).

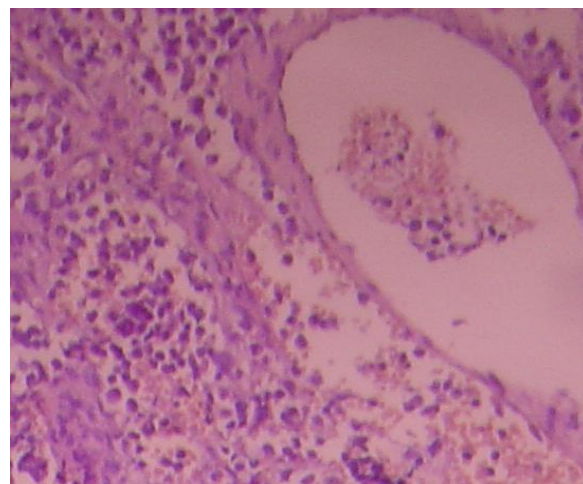


Figure 1. Sino-nasal mucosal malignant melanoma, histopathological image (HE staining 40 × 10).

His FDG PET CT showed lymphadenomegalies in the neck, the biggest one being 3 cm. After two cycles of temozolamide treatment, the biggest lymphadenomegaly was measured as 5.5 cm in the neck. Radiotherapy was initiated for the head and neck region of the patient due to the progression and severe head pain (figure 2).

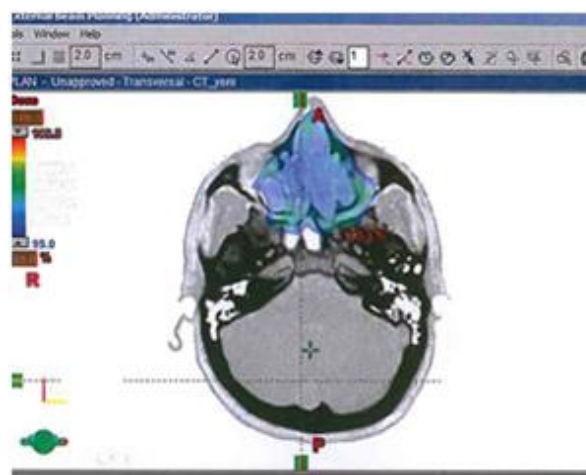


Figure 2. Sino-nasal mucosal malignant melanoma; Dynamic IMRT (Intensive modulation radiotherapy) isodose curves.

Radiotherapy was planned with CT simulation, fraction of 200 cGy with dynamic IMRT once a day and five days a week. In a control CT at a tumour dose of 4600 cGy, 50% regression was seen and a decision was made to continue radiotherapy, which was stopped at a total dose of 6600 cGy (figure 3).

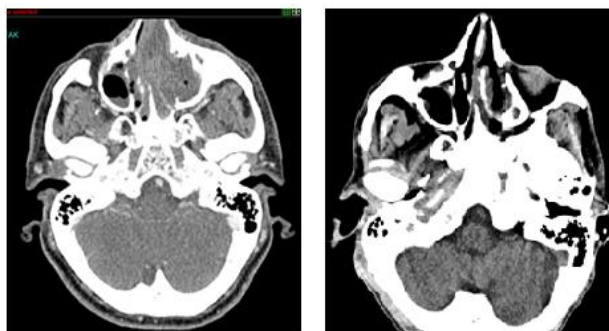


Figure 3. Sino-nasal mucosal malignant melanoma, the primary tumour; images before and after radiotherapy.

A full pain relief was achieved. During the course of treatment, radiotherapy was delayed for one week due to grade 3 oral mucositis, esophagitis, grade 2 skin reaction and dryness of the mouth.

After the treatment, in the control paranasal CT, a full response was seen to be obtained in the primary tumour. However, adrenal and lung metastases were appeared and the patient died 7 months later.

Discussion

Nasal mucosal melanoma is a very rare and aggressive melanoma type.¹⁻³ The best outcomes are obtained by surgery with postoperative radiotherapy in operable cases. Even with this therapy, the mean 5-year survival rate is around 10-40% in early stages.^{9-12, 26}

In early stage mucosal malignant melanoma, generally, a 50-75% onset response was reported to be achieved with radiotherapy.^{26,27} In metastatic melanoma, 21% response was achieved with temozolomide treatment.²⁸ In our metastatic sinonasal mucosal melanoma case, disease was progressed after temozolomide treatment. Survival was only 7 months with radiotherapy, while achieving a full response in the primary tumour and pain control. However, when compared with the literature, a survival duration above the average was seen for a metastatic sinus-nasal mucosal melanoma with skull base involvement.²⁹

One of the most important reasons for chemoresistance in nasal mucosal malignant melanomas is the inadequacy of apoptosis; and one of the most important reasons for this is lack of oxygenation in the tumour.³⁰ A good local control may be obtained with radiotherapy, but survival advantage has not been demonstrated with radiotherapy alone.¹⁸

In recent years, favourable results have been obtained with Src inhibitors. The Src inhibitors dasatinib and bosutinib can be used alone or with chemotherapy.³¹ Vemurafenib and ipilimumab are promising drugs that are recently approved for melanoma treatment.³²⁻³⁴

There is a great need for multicenter studies as the disease is rarely encountered.

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