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Secondary non-Hodgkin lymphoma of the ethmoid sinus after temozolomide

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Abstract. *Secondary non-Hodgkin lymphoma of the ethmoid sinus after temozolomide*. The paranasal sinuses are rarely the site of malignancy, especially non-Hodgkin lymphoma. In such cases, the ethmoid sinus is the second most frequently involved paranasal sinus. Diagnosis of these malignancies is difficult because the early symptoms often mimic benign sinus pathology. Thus, most cases are diagnosed at an advanced stage, and their prognosis is poor. Here we describe the case of a 58-year-old man with a secondary high-grade B-cell non-Hodgkin lymphoma of the ethmoid sinus. This malignancy was diagnosed two years after the patient had received treatment with temozolomide for a glioblastoma multiforme. This case highlights that malignant tumours of the paranasal sinuses should always be included in the differential diagnosis of sinus disease. Additionally, patients treated with temozolomide should receive regular follow-up care including vigilant evaluation for secondary tumours, such as non-Hodgkin lymphoma.

Introduction

Malignant tumours of the paranasal sinuses are uncommon, constituting only approximately 3% of all head and neck cancers and 1% of all malignancies.[1,2] Such tumours are often not diagnosed until they are at an advanced stage with invasion of adjacent structures, which impedes curative treatment and causes poor prognosis.[1,3] The present report describes the case of a patient with secondary non-Hodgkin lymphoma (NHL) of the ethmoid sinus following treatment with temozolomide for a glioblastoma multiforme.

Case report

In February 2012, a 58-year-old man was admitted to the emergency department with fever, headache, left-sided nasal obstruction, and purulent rhinorrhea. He also had a long-standing left eye infection that had not improved with the local application of oxytetracycline hydrochloride (Terramycine®). He had no other relevant medical history.

Chest X-ray revealed pneumonia, and treatment was initiated with a combination of antibiotics: amoxicillin-clavulanic acid, trimethoprim, and sulfamethoxazole. A CT scan of the brain and paranasal sinuses showed prominent pansinusitis and a contrast-enhancing mass breaking through the ethmoidal sinus into the left orbit, causing proptosis (Figures 1, 2). The patient showed progressive

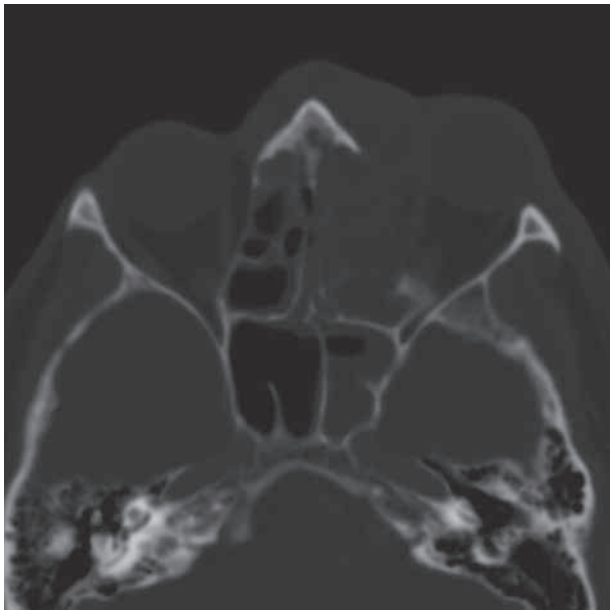

Figure 1
Axial CT scan (bone window) showing cortical destruction of the lamina papyracea and ethmoid cells on the left side.

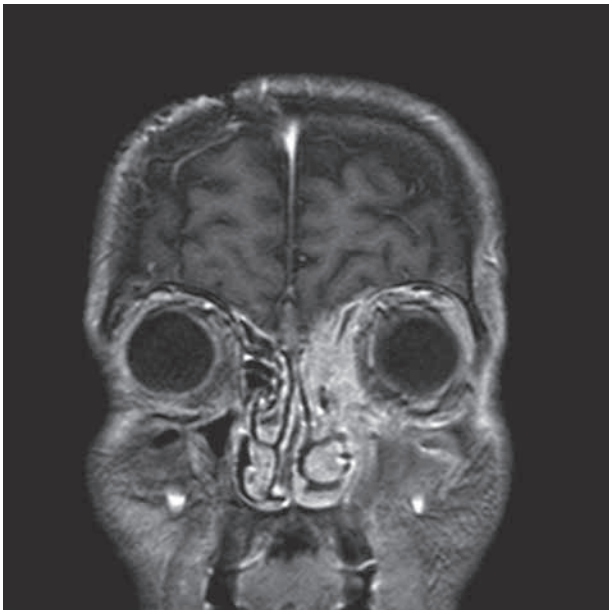

Figure 2
Pre-chemotherapy coronal T1-weighted MRI scan (TSE 2,35/TR 166,2) after gadolinium administration. A contrast-enhancing mass is visible in the left ethmoid sinus, invading through the left lamina cribrosa and left lamina papyracea with intra-orbital extension.

swelling and spontaneous fistulisation of the medial portion of the left superior eyelid.

An ENT surgeon performed nasendoscopic surgical drainage with removal of all visible pathologic tissue, which was found on the left side in the middle meatus, and in the maxillary, anterior, and posterior ethmoid sinus. A frozen section biopsy was taken perioperatively, and was suspected to be malignant with the presence of atypical cells. Postoperatively, a Penrose drain was left in place at the fistulisation route to allow frequent rinsing of the wound with ofloxacin drops (Trafloxal®; 3 mg/mL). After removal of the drain, the skin healed with minimal scarring.

Histopathologic examination of the biopsy sample confirmed the diagnosis of a stage IV high-grade diffuse large B-cell lymphoma (DLBCL). Such malignancies are often seen in immunodeficient patients, but viral serology showed no infection with HIV or hepatitis and revealed the presence of antibodies against cytomegalovirus or Epstein-Barr virus without indication of current infection. Further staging through PET-CT scanning showed that the lesion extended from the left ethmoid and maxillary sinus to the left nasal cavity, nasopharynx, and oropharynx. Bone marrow investigation showed dysplasia in all three lineages, but no signs of invasion.

In May 2010, the patient had been diagnosed with a glioblastoma multiforme (WHO grade IV). At that time, he was treated with concomitant external beam radiotherapy (60 Gy in 30 fractions) and temozolomide (TMZ) 75 mg/m^2/day over a period of 6 weeks, followed by adjuvant treatment with TMZ 150 mg/m^2/day for 5 days of an 28-day cycle. Despite this treatment schedule, MRI after 2 cycles revealed tumour progression and an extended dosing schedule was started: TMZ 100 mg/m^2/day for 21 consecutive days of a 28-day cycle. The patient underwent a total of 14 cycles of extended dosing with TMZ. Treatment was stopped in December 2011 when the planned fifteenth cycle was impeded due to persistent neutropenia. TMZ is an oral DNA-alkylating agent used to treat high-grade astrocytoma or glioblastoma multiforme and melanoma. The literature includes descriptions of a few cases of secondary haematological malignancies (i.e. non-Hodgkin lymphoma) occurring after treatment with TMZ.

Meanwhile, in April 2012, after the diagnosis of NHL, treatment with R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin, and predisone) was initiated with a 50% dose reduction. The patient poorly tolerated the first administration, experiencing nausea, vomiting, and the development of a disseminated zona with a painful skin rash and blisters due to the Herpes zoster virus. Follow-up imaging showed glioblastoma progression with two new lesions in the brain (parieto-occipital on the right side and parietal on the left side). In mid-April 2012, stereotactic radiosurgery with a single dose of 18 Gy was performed on these two lesions. Due to further clinical deterioration, the patient and his family decided to stop active treatment and proceed only with comfort therapy. The patient died four weeks later.

Discussion

Lymphomas are neoplasms that originate from cells of the lymphoreticular system. There are two main types of lymphoma. One type is Hodgkin lymphoma (HL), which is of B-cell origin and characterised by the presence of multinucleated Reed-Sternberg cells on histopathologic examination. The other type, non-Hodgkin lymphoma, constitutes 60% of

lymphoma and is classified into B- and NK/T-subtypes according to lymphocytic phenotype. People with NHL show overall 5- and 10-year relative survival rates of 69% and 58%, respectively.[4,5]

Both primary and secondary lymphomas of the paranasal sinuses are most commonly NHL.[5] In Western populations, sino-nasal tract lymphomas account for 0.2-2% of all NHL,[6] with B-cell lymphomas being more common and predominantly affecting paranasal sinuses. In contrast, Asian populations more frequently show nasal cavity lymphomas, which are predominantly NK/T-cell lymphomas.[4,5] These malignancies account for 2.6-6.7% of all lymphomas and are the second most frequent type of extranodal lymphoma, after gastrointestinal lymphoma.[6] NK/T-cell lymphomas are relatively more resistant to chemotherapy and are frequently associated with Epstein-Barr virus infection, also called human herpesvirus 4.[4,5,7] Approximately 10-34% of all NHL arise in extranodal sites, with less than 3% presenting in the sino-nasal region.[8] Among patients with DLBCL, extranodal involvement is considered a poor prognostic factor.[9]

In an earlier study, Chaltras *et al*.[4] report 12 patients with NHL of the nasal cavity and paranasal sinuses (7 males and 5 females; mean age, 62 years). The most frequent histologic type was DLBCL and the mean 5-year survival rate was 50%. Another study published by Li *et al*.[7] included 175 patients with primary NHL of the nasal cavity, of which 63 patients had paranasal extension in the ethmoid sinus. The overall 5-year survival rate was 65%. Peng *et al*.[10] reviewed 17 cases of sino-nasal lymphoma, and reported that maxillary and ethmoid sinuses were more frequently affected and that DLBCL was the most common histologic type (53%). The 2-year and 5-year overall survival rates were 75% and 53%, respectively, and the disease-free 2-year and 5-year survival rates were 70% and 49%, respectively.

In the presently reported case, the patient developed an NHL in the ethmoid sinus after extended dosing treatment with TMZ for a glioblastoma multiforme. TMZ is an oral DNA alkylating agent that causes depletion of the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT). It is increasingly used in the treatment of newly diagnosed glioblastoma and recurrent glioma.[11] Alkylating agents suppress the immune system and have a mutagenic effect as the MGMT depletion causes defective DNA repair. This predisposes the patient to the development of secondary haematological neoplasms and solid tumours, such as myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), and NHL.[12] TMZ reportedly has a less myelotoxic profile than traditional chemotherapy, but the reported haematological adverse events and secondary malignancies raise substantial concerns regarding its increasing use. Villano *et al*.[13] reported that aplastic anaemia occurrence appears unique to TMZ among alkylating agents, and is seen even with a short duration of prior TMZ exposure. The risk of AML and MDS appears to be relatively low.[13]

Only a few cases of secondary NHL following TMZ treatment have been previously described in the literature.[11,12,14,15] Neyns *et al*.[11] reported three cases in which a secondary NHL developed after glioma treatment with TMZ. The first patient was a 53-year-old female who was diagnosed with a DLBCL of the neck 7 months after the end of TMZ therapy. The second and third patients were both 48-year-old males. At 1 year after TMZ administration, the second developed a DLBCL of the stomach and the third developed a mucosa-associated lymphoid tissue lymphoma (MALT). In another report, Sharma *et al*.[12] described the occurrence of a disseminated Burkitt lymphoma in a 20-year-old female 2 months after treatment with TMZ for a glioblastoma multiforme. Finally, Otty *et al*.[15] described a 68-year-old male who was treated with TMZ for a glioblastoma multiforme and subsequently developed an NHL of the left cheek that was successfully treated with chemotherapy.

Conclusions

The present case report highlights the importance of regular follow-up care for patients treated with TMZ, to ensure early detection of haematological adverse events and secondary malignancies. Moreover, lymphoma should always be included in the differential diagnosis of sinus disease or tumours. The presently described case was exceptional because the NHL presented after previous exposure to TMZ for the treatment of a high-grade glioblastoma multiforme. This is the first reported case of an NHL in the ethmoid sinus after treatment with TMZ.

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