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SECONDARY MALIGNANCY IN GIANT CELL TUMOR OF THE SKULL BASE AFTER DENOSUMAB TREATMENT: CASE REPORT

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Abstract

Giant cell tumor of bone is a rare neoplasm characterized by its unpredictable behavior, possible malignant transformations, and/or lung metastases. Surgery is the treatment of choice. In unresectable or metastatic cases, treatment with denosumab is a new treatment option.

In October 2015, a 14-year-old female presented with cachexia, dysphagia, diplopia, discoordination, strabismus, and multiple cranial nerve palsies. An MRI examination revealed an intra-extracranial mass arising from C2 vertebrae, compressing the medulla oblongata and the left cerebellar hemisphere, invading the sphenoid bone and nasopharynges. The biopsy results revealed the presence of a giant cell tumor of bone. The first surgical resection was incomplete because of tumor location (cranial nerve and vertebral artery involvement). The patient received local radiotherapy with 50.4Gy, but the patient's condition worsened during this period and subsequent MRI examination showed disease progression. In March 2016, the administration of denosumab at a dosage of 120 mg every 4 weeks was initiated, and induced rapid clinical improvement and radiographically proven partial response. Disease was under control for three years until March 2019, when she returned with clinical symptoms of diplopia and severe headache. MRI showed local tumor progression. Repeated biopsy revealed an undifferentiated pleomorphic sarcoma. Two cycles of chemotherapy with Ifosfamide/Doxorubicin were administered, but MRI after chemotherapy showed marked tumor progression. The patient received palliative care and died due to disease progression in December 2019 – 4 years after initial diagnosis.

To our knowledge, this is the youngest patient ever reported with a skull base Giant cell tumor initially responding to denosumab for 3 years but progressing to chemotherapy resistant undifferentiated pleomorphic sarcoma.

Keywords: *secondary malignancy, giant cell tumor of bone, GCT, denosumab.*

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Introduction

Giant cell tumors (GCTs) of bone are rare and primarily benign osteoclastogenic tumors of stromal origin. They account for approximately 5% of primary bone tumors. Giant cell tumors are diagnosed most frequently among young adults, and are uncommon in younger children [*Luengo-Alonso G et al., 2019*].

Giant cell tumors are mainly locally aggressive. Rarely they can metastasize (e.g. to the lungs in 5% of cases) or transform into malignant tumors (less than 0.4-1%) [*Luengo-Alonso G et al., 2019*] presumably due to previous radiation or occasionally long-term denosumab use, even though there are reported cases of malignant transformation without previous treatment [*Dahlin D et al., 1970; Skubitz K, 2014; Alaqaili S et al., 2018*].

Clinically these tumors may cause pain, loss of productivity, impaired mobility and may even be life-threatening or limb-threatening depending on their anatomical site such as the base of the skull, vertebra, etc. [*Thomas D et al., 2010*].

The most common locations are distal femur, proximal tibia, distal radius, and fibula [*Sobti A et al., 2016*]. These tumors affect the spine in about 9% of cases, and are rarely located in the cranial base. The recurrence rate of GCTs of the spine is 25-50% [*Lin P et al.,2018*].

Histologically, the tumor is composed of multinucleated giant and mononuclear stromal cells. The latter compose neoplastic component of the tumor and precursor cells of the mesenchymal osteoblasts. These osteoblastic stromal cells express receptor activator of NF-kappa B ligand (RANK-L), the excessive expression of which results in osteoclast activation, and thus, bone lysis and destruction [*Luengo-Alonso G et al., 2019*]. Therefore, the monoclonal antibody denosumab, which inhibits RANKL, has therapeutic effects in GCT.

Treatment options for GCTs depend on tumor size and localization. Surgical resection is considered the primary curative method [*Skubitz K, 2014*]. Before denosumab era, radiotherapy has been used as an alternative treatment for unresectable and recurrent GCTs. Radiotherapy may be also used as adjuvant therapy after incomplete resection with positive or uncertain margins [*Caudell J et al., 2003*].

Denosumab has been approved for the treatment of adults and adolescents with GCTs of bone that are unresectable due to location or size or when surgical resection is likely to result in mutilation. However, patients are at an increased risk of relapse after ceasing denosumab, thus, a reduced dose of denosumab or the less frequent administration of the drug for maintenance in patients with unresectable disease may be considered [*Luengo-Alonso G et al., 2019*].

Malignant transformations are very uncommon in GCTs and were first recorded 80 years ago [*Stewart F et al., 1938*]. According to Chawla S. and co-authors (2013) no evidence exists to support a causal association between secondary malignancy and denosumab treatment. However, recent reports challenge this statement [*Skubitz K, 2014*; *Tsukamoto S et al., 2017*]. In addition, findings suggest that careful radiological and pathological evaluation of the tumor is warranted before treatment; H3.3 Histone A (*H3F3A)* mutation testing can be useful to differentiate GCTs of bone from giant cell-rich sarcomas.

Herein we provide a follow-up report on a 14-years-old female with GCT of skull base who has received initial unsuccessful treatments by surgery and radiotherapy, had excellent clinical response to denosumab [*Bardakhchyan S et al., 2017*], but developed malignant transformation 3,5 years after diagnosis and died from rapid progressive undifferentiated pleomorphic sarcoma.

Case Presentation

In October 2015, a 14-year-old female presented with cachexia, dysphagia, diplopia, discoordination, strabismus, and multiple cranial nerve palsies. A magnetic resonance imaging (MRI) examination revealed an intra-extracranial mass arising from C2 vertebrae, compressing the medulla oblongata and the left cerebellar hemisphere, invading the sphenoid bone and nasopharynges. The biopsy results revealed the presence of a giant cell tumor of bone. The first surgical resection was incomplete because of tumor location (cranial nerve and vertebral artery involvement). The patient received local radiotherapy with 50.4Gy, but the patient's condition worsened during this period and subsequent MRI examination showed disease progression [*Bardakhchyan S et al., 2017*].

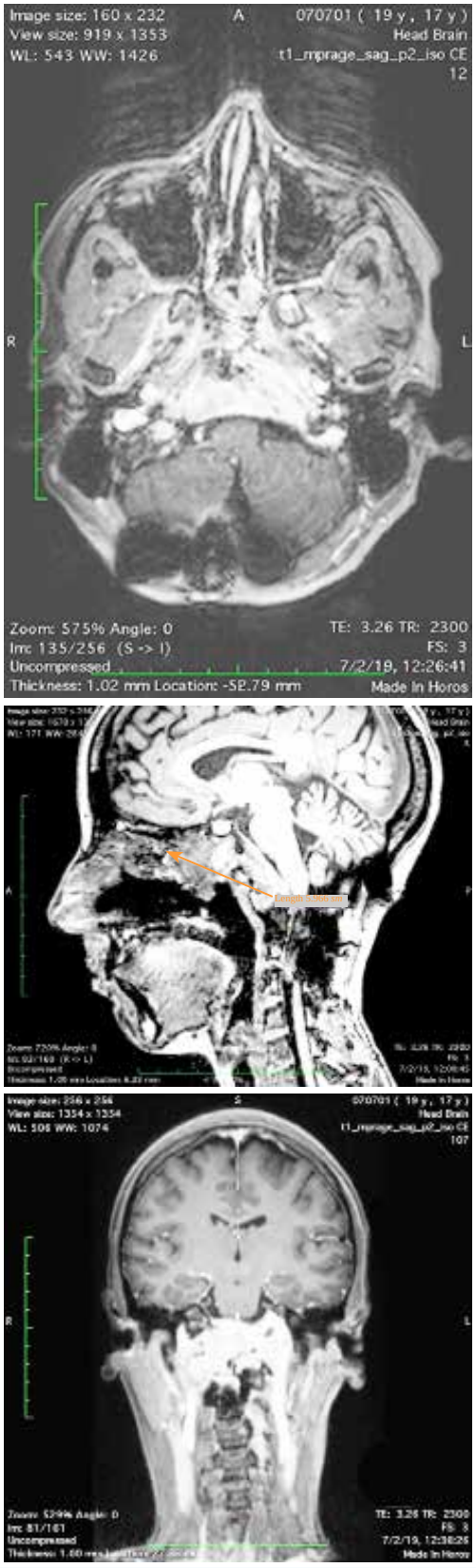

FIGURE 1. *MRI at progression before the start of chemotherapy*
(A) axial, (B) coronal and (C) sagittal images of T1 weighted MRI after contrast admision performed at tumor progression revealed skull base large mass with massive destruction of the bony structures, surrounding large vessels, which enhances after contrast injection

In March 2016, the administration of denosumab at a dosage of 120 mg every 4 weeks was initiated, and this yielded successful results and patient's clinical condition improved drastically after few injections of denosumab. MRI done after four cycles of denosumab treatment confirmed tumor regression (3,2×6,8×5,2*cm*), which was suspected from the delectable clinical course [*Bardakhchyan S et al., 2017*].

The patient was receiving maintenance denosumab every month and was tolerating it rather well without any severe adverse effects. Regular MRIs were showing stable course of disease for 3 years (until March 2019).

In March 2019 the patient returned with symptoms of diplopia and uncontrolled headache, which required opioid analgesics. MRI evaluation showed growth of the residual tumor (Fig. 1).

Biopsy was done and revealed another cancer: an undifferentiated pleomorphic sarcoma (Vimentin+, CD10+, CD99+, p53+, S100+, CD68+, SMA-, Ki67 65-70%) (Fig. 2).

CT scan didn't show any distant metastatic lesions.

Chemotherapy was initiated with Ifosfamide

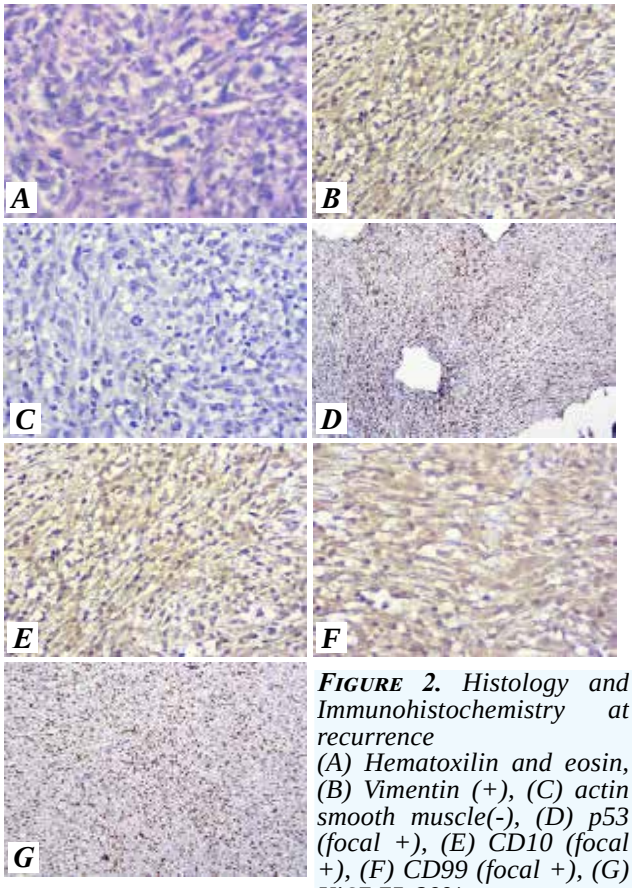

FIGURE 2. *Histology and Immunohistochemistry at recurrence*
(A) Hematoxilin and eosin, (B) Vimentin (+), (C) actin smooth muscle(-), (D) p53 (focal +), (E) CD10 (focal +), (F) CD99 (focal +), (G) Ki67 75-80%

(2500*mg/m*^{2} for 4 days) and Doxorubicin (25*mg/m*^{2} for 3 days). Immediately after the first cycle of chemotherapy headaches attenuated and became manageable without usage of narcotic painkillers. Unfortunately, soon after the first cycle, she developed severe pancytopenia, stomatitis, esophagitis, and afterwards bilateral pneumocystic pneumonia with left sided pneumothorax. Chemotherapy was interrupted. After a month of recovery, the headaches returned. The second chemotherapeutic cycle was administered with 25% reduction of the drug doses, but this time, the therapy was ineffective, and MRI showed massive tumor progression with a large invasive formation (7.5×6.5×5.5*sm*) affecting sphenoid and ethmoid sinuses, nasal cavity, nasopharynx, para, and retropharyngeal, masticatory, and carotid spaces on the right side, with extension to intracranial space and infiltration of the right cavernous sinus. The tumor also infiltrated the basis of the cranium and the cranio-vertebral junction (Fig. 3).

The patient became cachectic, was suffering severe headaches requiring opioids and had severe dysphagia requiring enteral feeding via a nasogastric tube. It was decided to stop active chemotherapy and patient was discharged with palliative care at home. She passed away due to disease progression in December 2019, at the age of 18, 4 years after initial diagnosis.

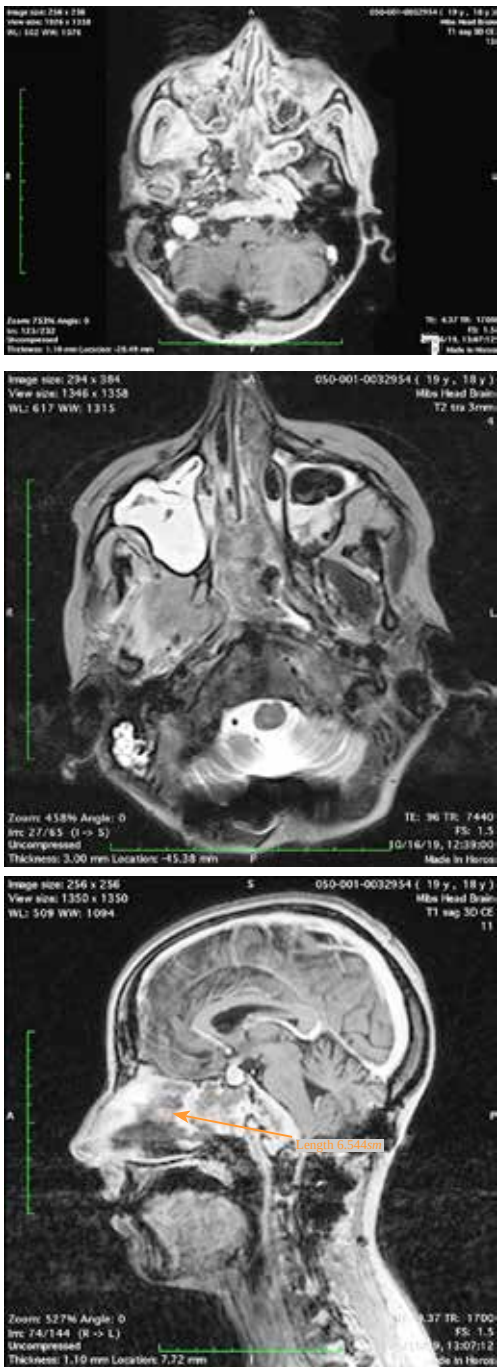

Figure 3. *MRI after 2 cycles of chemotherapy (A) axial, (B) coronal and (C) sagittal images of T1 weighted MRI after contrast admision performed after 2 cycles of chemotherapy revealed a large invasive formation of sphenoid and ethmoid sinuses, nasal cavity, nasopharynx, para and retropharyngeal, masticatory and carotid spaces on the right side, with extension to intracranial space, infiltration of the right cavernous sinus and large zone of ostelysis. The tumor also infiltrates the basis of the cranium and the cranio-vertebral junction. The mass has grown in size in comparison with 02 July 2019 MRI examination, up to 7.5×6.5×5.5 cm in size*

Discussion

Giant cell tumors as a benign, locally aggressive growing bone tumors are commonly diagnosed among adults aged 20-40 years with female predominance. These tumors are most often located in the distal femur, proximal tibia, distal radius or fibula [*Sobti A et al., 2016*]. The skull base and spine are not common locations for GCTs [*Lubicky J et al., 1983*]. The incidence in the cervical spine is even more uncommon and makes for less than 1% of all the cases of GCTs [*Santiago N et al., 2012*].

The GCTs may undergo malignant transformation: mostly to osteosarcoma, fibrosarcoma, or undifferentiated pleomorphic sarcoma (historically known as malignant fibrous histiocytoma) [*Palmerini E et al., 2019*]. Malignant transformation in GCTs may be primary (presence of a malignant pleomorphic nodule in the

tissue of GCT during initial diagnosis) or secondary (development of the secondary malignancy after treatment of nonmalignant GCT). Primary malignant transformations are evident at first diagnosis of GCT and contain an area or a nodule of highly pleomorphic mononuclear cells present within an otherwise conventional GCT. Although rare, such cases are reported in the literature [*Palmerini E et al., 2019*]. Secondary transformations occur at the site of previously treated GCT, and the preexisting GCT may or may not be evident [*Stewart F et al., 1938; Alaqaili S et al., 1970*] Most sarcomatous transformations are secondary and typically follow radiotherapy [*Tsukamoto S et al., 2017*], but on very rare occasions they can follow surgery without adjuvant radiotherapy [*Palmerini E et al., 2019*]. Earlier studies pointed out the role of irradiation in malignant transformation of GCTs, but radiotherapy with modern technologies and doses less than 50Gy has practically eliminated the risks [*Caudell J et al., 2003*]. Some recent studies are also reporting malignant transformation of GCTs after treatment with denosumab [*Alaqaili S et al., 2018*; *Li H et al., 2020*].

Among cases from the literature the malignant transformation of GCTs may occur at various times during or after the treatment. There are several reported cases, describing development of sarcoma short time after surgical treatment of GCT. Malignant transformations after surgery usually develop during the first two years of the treatment [*Dahlin D et al., 1970*]. Malignant transformation after radiotherapy is mostly occurring after much longer latent period: in a large series of studies Bertoni F. and co-authors (2003) reported 6 cases of malignant transformation of GCTs following radiation with the median latent period for transformation of 9 years (range 1.7-15 years) after radiotherapy. Some other studies give the range of 2.5-22 years after radiotherapy [*Feigenberg S et al., 2019*]. In comparison malignancies developing during denosumab therapy are very rare and earlier in their pattern (n=18 (19, considering our patient); mean 1.1 years, range 0.2-2.8 years) [*Li H et al., 2020*]. Some cases report malignant transformation of GCT treated with denosumab after an average of 1-year latent period [*Aponte-Tinao L et al., 2015*; *Alaqaili S et al., 2018*]. The literature only reports 18 patients who developed secondary malignancy during denosumab treatment and only one of them was under 18 years old at the time of diagnosis [*Aponte-Tinao L et al., 2015*; *Li H et al., 2020*]. This patient was diagnosed with GCT at the age of 15 and developed pleomorphic sarcoma after some unsuccessful surgical procedures and one year of treatment with denosumab (5 years after the initial diagnosis of GCT) [*Aponte-Tinao L et al., 2015*].

The potential mechanism of malignant transformation of GCTs after denosumab therapy might be associated with the diminished function of RANKL [*Tsukamoto S et al., 2017*], which, through different mechanisms may indirectly increase the risks of sarcoma development via immunosuppression [*Criscitiello C et al., 2015*]. Other potential mechanisms are semaphorin 3A gene knockout [*Behar O et al., 1996*] and increased sensitivity of nuclear oncogenes [*Mori K et al., 2007*].

Moreover, malignancy development is extremely rare among pediatric patients, especially after such a short time after the diagnosis as in our case (3.5 years after the initial diagnosis). Our literature review has identified only six reported cases (including our own) of patients aged 19 or younger who have experienced secondary malignant transformation following a diagnosis of GCT (Table) [*Rock M et al., 1986*; *Picci P et al., 2011*; *Gong L et al., 2012; Aponte-Tinao L et al., 2015*].

Conclusion

This report outlines the follow-up of a teenage patient with a progressive skull GCT. The initial treatment involved the successful administration of denosumab, as reported in the Italian Journal of Pediatrics [*Bardakhchyan S et al., 2017*]. Unfortunately, the patient developed undifferentiated pleomorphic sarcoma at the site of the previously non-malignant, residual GCT 3.5 years after receiving radiotherapy and during the course of denosumab treatment (3 years after initiation of treatment). The likelihood of an initial misdiagnosis of GCT in our case is low for two reasons. Firstly, the tumor biopsy and subsequent surgical resection, along with complete histologic and immunohistochemistry examinations, confirmed the diagnosis of GCT without any sarcomatous features. Secondly, the patient's symptoms resolved fol-

Table

Patients aged 19 or less diagnosed with malignant transformation of bone giant cell tumor

Authors	Gender	Age (*years*)	GCT location/ developed malignancies	Time to malignancy from the diagnosis (*years*)	Duration of denosumab therapy (*years*)	Radiation therapy	Number of surgeries
Aponte-Tinao L. et al., 2015	female	15	Proximal tibia/ pleomorphic sarcoma	5	1	-	2
Picci P et al., 2010	male	13	Proximal femur/undifferentiated pleomorphic sarcoma	20	-	-	Unknown 1 or 2 amp+chemo
Rock G et al., 1986	female	17	Distal femur/Grade 4 fibrosarcoma	16	-	"deep" radiation therapy	1
Gong L et al., 2011	male	17	Distal humerus/ osteosarcoma	n/a	-	-	n/a
Picci P et al., 2010	male	19	Proximal tibia/ undifferentiated pleomorphic sarcoma	27	-	-	2/amp+chemo

Notes: *GCT= giant cell tumor, n/a = not available, - = not received*

lowing the initiation of denosumab treatment. The remarkable aspects of our case include the rare location of the tumor, the occurrence of sarcoma 3.5 years after the initial diagnosis, and the patient's young age.

However, there is insufficient evidence to ascertain the cause of the malignancy development. It remains uncertain whether the malignancy development can be referred to denosumab therapy, radiotherapy, or other factors.

We expect this discovery to make a valuable contribution to the existing literature on this topic and suggest the conduction of comprehensive large-scale studies to investigate the safety of administering high doses of denosumab for the treatment of bone GCTs.

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