

Malignant Giant Cell Tumor of the Sphenoid

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Malignant giant cell tumors (MGCTs) of the sphenoid sinus are extremely rare neoplasms. They are challenging to diagnose and difficult to treat because of their skull base location. To the best of our knowledge, we report the first case of a primary MGCT of the sphenoid arising in a patient with Paget's disease. A 77-year-old man presented with epistaxis and a history of Paget's disease. There was normal cranial nerve function although radiographic images disclosed a large mass centered in the sphenoid sinus and extending into the ethmoid and maxillary sinuses. Excisional biopsy revealed a MGCT composed of a cellular stroma with increased mitotic activity and necrosis with giant cells present throughout. Additional therapy was declined and the patient died with disease 7 months later. Because of their rarity, no treatment guidelines exist for the management of MGCTs of the sphenoid. We discuss both the diagnostic and therapeutic considerations based on a review of the pertinent literature.

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PRI-MARY malignant giant cell tumors (MGCTs) are uncommon neoplasms that develop primarily in the metaphyseal region of long bones in the appendicular skeleton.¹ A number of benign giant cell tumors (GCTs) arising in the sphenoid bone have been reported,²⁻¹⁴ occasionally associated with Paget's disease,⁴ with a single report of malignant transformation after radiotherapy.⁷ Primary MGCTs of the craniofacial skeleton are exceedingly rare, with, to the best of our knowledge in a review of the English literature (MEDLINE 1966-2002), only one confirmed case reported arising in the sphenoid sinus.¹⁰ We present the second

case report of a primary malignant giant cell tumor of the sphenoid, and the first report of a case arising in a patient with Paget's disease, along with a review of the pertinent English literature.

Materials and Methods

A case diagnosed as MGCT was retrieved from the files of the Otorhinolaryngic-Head and Neck Pathology Registry at the Armed Forces Institute of Pathology (Washington, DC) between 1970 and 2001. This patient was identified in a review of 24,481 (0.004%) benign or malignant primary sinonasal tract tumors seen in consultation during this time. Materials within the Institute's files were supplemented by a review of the patient's clinical record, operative report, and surgical pathology reports. Additional clinical details and follow-up was obtained from the treating physicians. Hematoxylin-eosin-stained slides were reviewed to confirm the diagnosis. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and Department of Defense Directive 3216.2 relating to human subjects in research.

Case Report

A 77-year-old black man presented with a 1-week history of recurrent epistaxis and headache. His past medical history was significant for polyostotic

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Paget's disease (osteitis deformans), diabetes, chronic obstructive pulmonary disease, hypertension, and developmental delay. Social history was unremarkable for alcohol or tobacco use. Physical examination revealed craniofacial dysmorphic features, an absence of sinus or facial tenderness, normal extra-ocular movements, and normal neurologic examination including the cranial nerves. Endoscopic nasal examination showed an erythematous right nasal mass filling the entire nasal cavity with a bloody, purulent discharge. Computer tomography of the sinuses showed an expansile mass centered in the sphenoid sinus, obliterating the sphenoid and ethmoid sinuses and eroding through the lamina papyracea on the right (Fig 1). There was also diffuse enlargement of the skull base and facial bones (including the sphenoid wings, ethmoid bones, zygoma, maxilla, frontal, and parietal bones) with cortical and trabecular thickening consistent with Paget's disease (Fig 1). Tissue cultures obtained at the time of biopsy failed to yield any infectious agents (bacteria, fungi, or viruses). The excisional biopsy of the mass revealed a diffuse infiltrate of the soft tissues by rounded to spindled mononuclear cells with osteoclastic giant cells (Fig 2). A thin shell of bone was identified at the periphery, demonstrating the characteristic

“mosaic” remodeling of Paget's disease of bone. The tumor was composed of a cellular, loosely cohesive mononuclear component with areas of tumor cell spindling, necrosis, and increased mitotic figures ($> 10/10$ high power fields; Fig 3). Atypical mitotic figures were noted. The necrosis was focal, “comedo-like,” and found between the giant cells. There was moderate to severe nuclear pleomorphism of the stromal cell nuclei, which were histologically identical to those found in the giant cells. The giant cells were scattered evenly throughout the tumor, with the giant cells containing from 10 to over 100 uniform, round to ovoid nuclei, indistinguishable from the nuclei of the stromal cells (Fig 4). Therefore, if the nuclei of the stromal cells were atypical, so were those in the giant cells. The entire proliferation was separated into small groups by a delicate, complex, and arborizing vascular plexus. Extravasated erythrocytes, hemosiderin-laden macrophages, and areas of hemorrhage were noted. Based on the remarkably increased cellularity, cytologic pleomorphism, tumor necrosis, increased mitotic activity, and atypical mitotic figures, a diagnosis of MGCT was rendered.

The patient and his family elected no further therapy because of his frail overall physical condi-

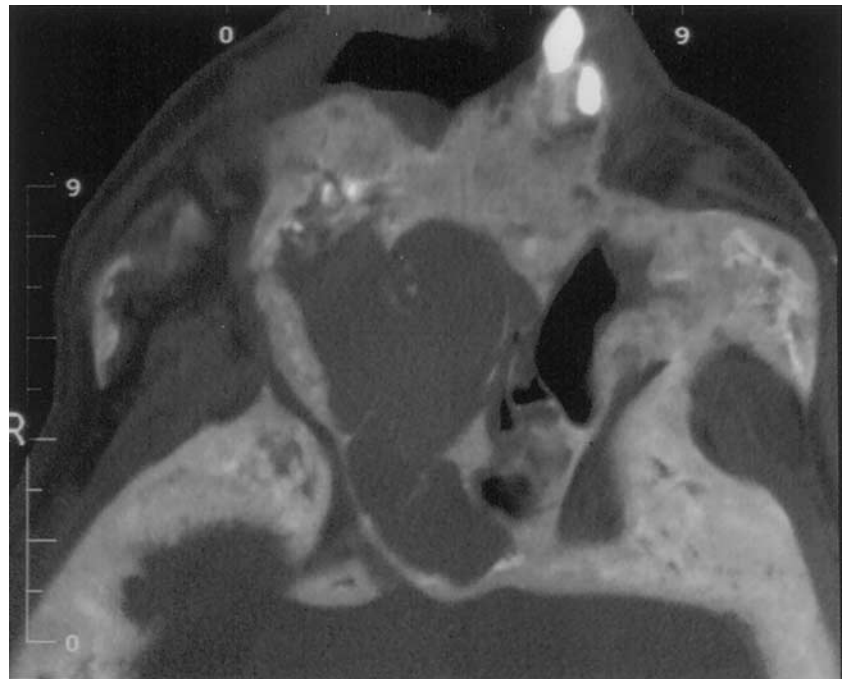


Figure 1. A computerized tomography scan demonstrates opacification of the bone to include the sinuses, a finding characteristic for Paget's disease of bone. There is an expansile mass destroying the sphenoid and ethmoid sinus with extension into the maxillary sinus.

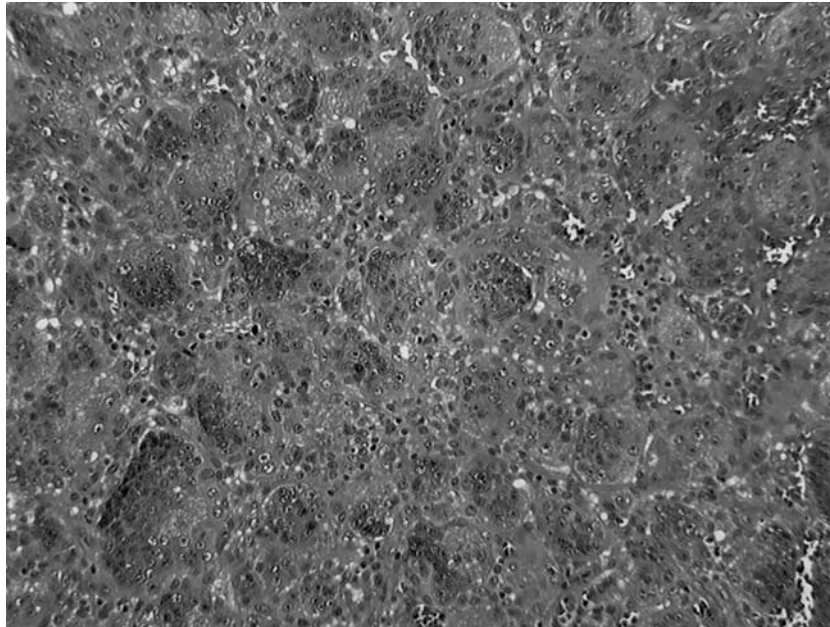


Figure 2. A low-power micrograph showing a proliferation of the cellular mononuclear stromal component with a sprinkling of giant cells throughout. (Hematoxylin-eosin stain; magnification $\times 30$.)

tion. He died 7 months later from sepsis and a cerebrovascular accident (stroke), unrelated to the tumor, although the tumor was still present, without evidence of disseminated disease.

Discussion

Most of the cases of GCTs of the sphenoid sinus reported in the literature are benign.²⁻¹⁴ Primary

MGCT presenting with aggressive and malignant behavior from the onset are extremely uncommon, even in the long bones of the appendicular skeleton.¹⁵ To the best of our knowledge in a review of the English literature there is only one well documented primary MGCT arising from the sphenoid bone.¹⁰ One additional case report suggested possible malignant features by histology, but did not

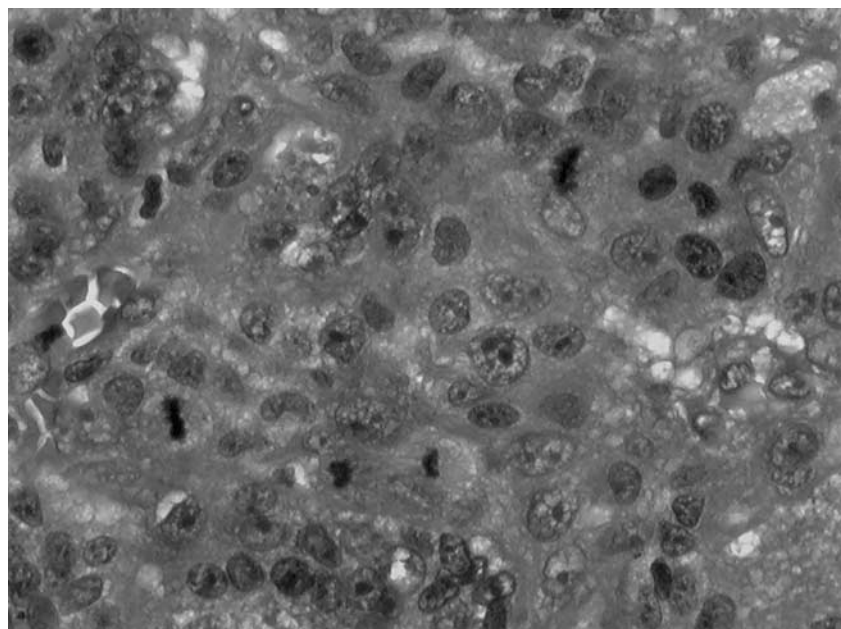


Figure 3. A high-power micrograph showing a remarkable number of mitotic figures accompanying osteoclast-type giant cells with nuclei similar to those of the stromal component. (Hematoxylin-eosin stain; magnification $\times 300$.)

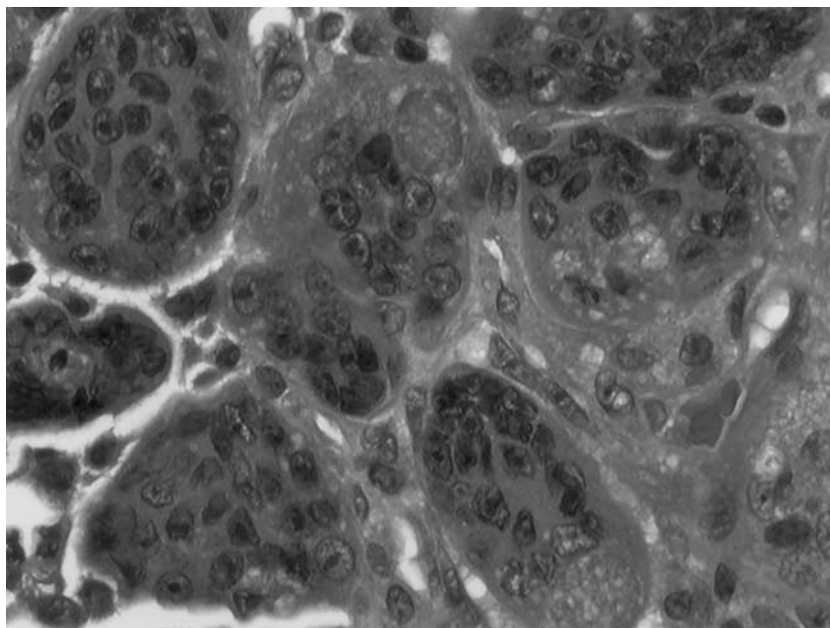


Figure 4. A high-power micrograph showing many nuclei within the giant cells. The nuclei contain prominent nucleoli. (Hematoxylin-eosin stain; magnification $\times 600$.)

have any patient follow-up.¹¹ There was a single case report of malignant transformation following radiation therapy in a GCT of the sphenoid bone.⁷ Finally, there is only one well-documented case of a sphenoid benign GCT arising in the setting of Paget's disease (see Table 1).⁴ Therefore, in summary, while a few MGCTs of the sphenoid sinus are reported, there is no case reported of sphenoid

MGCT arising in the milieu of Paget's disease of bone.

Because of their scarcity, limited information exists regarding the clinical presentation of GCTs of the sphenoid. Malignant giant cell tumors of the sphenoid would be expected to present initially in a manner similar to their benign counterparts, with nonspecific findings related more to their location

Table 1. Clinical Presentation and Patient Outcome of Cases Reported as Atypical or Malignant Giant Cell Tumors of the Sphenoid Sinus With or Without Paget's Disease Reported in the English Literature

| Case No. | Age/Gender | Location | Initial Therapy | Histology | Tumor Recurrence | Patient Status (Follow-Up in Years) |
|------------------|------------|------------------------------|----------------------------|-------------------------|--|-------------------------------------|
| 1 ¹⁰ | 41/M | Sphenoid | Biopsy; radiation (61 cGy) | Malignant GCT | No | DD (1.3) |
| 2 ⁷ | 20/M | Sphenoid | Biopsy; radiation (50 cGy) | GCT | Yes; malignant transformation; vincristine | DD (3) |
| 3 ¹¹ | 26/M | Sphenoid | Debulking | Possible malignant GCT | Unknown | LTF |
| 4 ⁴ | 68/M | Sphenoid, ethmoid, maxillary | Debulking | Paget's disease and GCT | No | A NED (0.5) |
| 5 (present case) | 77/M | Sphenoid, ethmoid | Biopsy only | Malignant GCT | Yes (residual) | DD (0.6) |

Abbreviations: GCT, giant cell tumor; A NED, alive no evidence of disease; DD, dead, with evidence of disease; LTF, lost to follow-up.

at the skull base and proximity to vital structures such as cranial nerves, dura, and orbit. The most commonly reported symptoms include headache, diplopia, epistaxis, visual field loss, proptosis, swelling, pain, cranial nerve palsies, obstruction or congestion, and nasal discharge.²⁻¹⁴ The patient in this report presented with epistaxis and headache, yielding no differences to benign GCTs in this location. Therefore, symptomatology alone cannot help to discriminate between benign and malignant GCTs.

Whereas GCTs do not usually have a gender predilection, it is interesting to note that the only cases involving the sphenoid sinus in which there is a background of Paget's disease and/or a malignant histology have all occurred in men (Table 1). It is well known that sarcomatous transformation in Paget's disease in all anatomic sites is more frequent in men.^{16,17} Furthermore, it also seems that while GCTs in general occur in younger patients, the sarcomatous transformation seems to occur more frequently in older patients.^{10,15-17}

Although uncommon, benign GCTs complicating Paget's disease have been reported, with the majority of them typically involving the craniofacial bones rather than the long bones.^{18,19} Although we identified very few GCTs of the sphenoid in Paget's disease of bone,⁴ this is (to the best of our knowledge) the first MGCT of this location to arise in Paget's disease. Several investigators have shown that GCTs arising in patients with Paget's disease are less aggressive than GCTs not associated with Paget's disease.^{4,20} However, there is usually an extremely poor overall prognosis (<10% 5-year survival) in the approximately 1% to 6% of patients with Paget's disease of bone who develop a sarcomatous transformation. The sarcomas are usually osteosarcoma or fibrosarcoma which tend to be resistant to radiation treatment.^{4,15-17} Malignant giant cell tumors are too uncommon to prove a particular outcome, although based on our review of the literature and the outcome of the patient in this case report, there seems to be a poor overall patient prognosis.

There is considerable deliberation in the literature about what constitutes a MGCT.^{1,15} However, MGCTs are best defined by the histologic presence of a GCT with destructive growth into bone, the presence of necrosis and hemorrhage, sarcomatous stroma present in the majority of the tumor volume, and increased mitotic activity (including atyp-

ical forms). The original classification of MGCTs by Jaffe et al¹ separated GCTs into three categories, representing a continuum from benign (grade I), to intermediate (grade II), to malignant (grade III). Histologically, grade III tumors demonstrate profound nuclear pleomorphism and a sarcomatous spindle cell stroma. The tumor in this report was described as locally invasive, with increased cellularity, cellular atypia (pleomorphism), and high mitotic activity, including atypical forms, which is diagnostic of a MGCT.

The histologic differential diagnosis for a MGCT of the sphenoid includes a benign GCT, giant-cell reparative granuloma, cherubism, fibrous dysplasia, ossifying fibroma, various pleomorphic sarcomas with osteoclast-like giant cells, and malignant osteosarcoma. Definitive diagnosis requires biopsy with histologic analysis because sphenoid tumors are impossible to differentiate solely on clinical or radiographic findings. Most of the differential diagnostic considerations can be eliminated by careful examination and correlation of the histologic findings with the radiographic studies. Cherubism and fibrous dysplasia have unique radiographic and clinical findings and little overlap with GCTs, except for occasional giant cells in all of the lesions. A giant cell reparative granuloma typically involves the mandible, characteristically has fewer giant cells of smaller size with few nuclei arranged haphazardly and unevenly in the tumor, a more fibroblastic stroma, and an absence of mitotic activity. Sarcomas with osteoclast-like giant cells generally have much fewer giant cells, the nuclei within the giant cells are not similar to those of the stroma, and contain a much more pleomorphic spindle cell component. Osteosarcoma is a common malignancy in patients with Paget's disease. The findings of osteosarcoma include a sunburst pattern on radiographic studies, a remarkably atypical osteoblastic proliferation, lace-like osteoid deposition, increased mitotic activity, and only occasional osteoclast-like giant cells.

The inherent challenge in treating neoplasms of the skull base is their location, rendering complete surgical excision difficult at best. Treatment options reported in the literature include various combinations of radiation and surgical therapy.^{9,12} The value of radiation therapy continues to be debated because GCTs were initially thought to be radioresistant and malignant transformation following radiation treatment has occurred.⁷ How-

ever, advances in radiation therapy have led to recent reports of its safety and efficacy in the management of GCTs, including those of the sphenoid.^{6,13} Because of the rarity of MGCTs of the sphenoid, no consensus on treatment or prognosis can be proposed. However, complete surgical excision to forestall local recurrence should be the goal, with radiation therapy reserved for unresectable or incompletely extirpated tumors.

Conclusion

Primary MGCTs of the sphenoid are rare neoplasms, especially in patients with Paget's disease. This tumor type has a nonspecific clinical presentation, an expansive and destructive growth radiographically, and characteristic (although somewhat controversial) histologic findings. Adequate excisional biopsy is required for diagnosis to exclude other neoplasms or reactive giant cell proliferations. Treatment options are limited, although complete surgical excision followed by radiation therapy for residual disease appears to yield the best overall outcome.

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