Giant cell tumor in the anterior cranial fossa – case report and systematic review

Review Article

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Abstract

Objectives: literature review on giant cell tumors of the bone (GCTB) involving the anterior skull base and case report of endoscopic endonasal surgical treatment.
Study Design: qualitative systematic review.
Materials and Methods: PubMed, BMC and Cochrane Library database review, based on the PRISMA MODEL. Iconographic description with images of the transcribriform endoscopic approach.
Results: 36 articles were selected and 21 GCTB involving the anterior skull base were identified. We present a case of TCGO centered on the cribriform plate, which underwent complete endoscopic endonasal excision at our institution.
Conclusion: according to the literature review, sinonasal GCTO with involvement of the anterior skull base are extremely rare, being this the second described originating from the cribriform plate. Although benign, it presented with aggressive behavior and complete surgical excision using and endonasal approach was carried out without complications.

Keywords: giant cell tumor, skull base, anterior cranial fossa, cribriform plate

Introduction

Giant cell tumor of bone (GCTB), characterized by the presence of multinucleated giant cells, was first described as “myeloid sarcoma” by Cooper and Travers in 1818. In 1910, Bloodgood introduced the term “benign giant cell tumor” but the word “benign” was later excluded after metastases were documented. In 1922, Steward proposed the term “osteoclastoma,” which eventually fell into disuse in favor of the currently accepted nomenclature—“giant cell tumor.”[1,2] GCTB accounts for 3–7% of all primary bone tumors, with a higher prevalence in females and individuals between 20–40 years of age. Approximately 75% of cases involve the

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Article received on April 25, 2024.
Accepted for publication on November 28, 2024.

epiphyseal region of long tubular bones, such as the femur, tibia, and radius. In contrast, GCTB develops in the skull in only 0.5–2% of cases, and predominantly affects the temporal, occipital, mandibular, and sphenoid bones.[3–8] The clinical presentation varies depending on the tumor location and extent, and may include symptoms such as headache, diplopia, amaurosis, altered sense of smell, epistaxis, facial paralysis, and hearing loss.[3,9]

Although GCTB is classified as a benign tumor, it can exhibit locally aggressive behavior and a high recurrence rate, particularly at the skull base where complete resection may be challenging, as well as pulmonary metastasis (4–5%) and malignant transformation into osteosarcoma (1–10%).[4,6]

Surgical resection is the primary treatment of GCTB. In cases with incomplete resection, adjuvant therapies such as radiotherapy or monoclonal antibodies (e.g., denosumab) may be employed.[3,10]

To further study this pathology, the authors conducted a systematic review of GCTB involving the anterior skull base. Additionally, we have presented a case of GCTB that was surgically treated via the endoscopic endonasal approach at our institution.

Materials and methods

A qualitative systematic literature review was conducted in January 2024 using the PubMed, BMC, and Cochrane Library databases, according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model. The following keywords were used: ("*giant cell tumor*" OR "*giant cell tumour*" OR "*osteoclastoma*") AND ("*skull base*" OR "*cribriform plate*" OR "*olfactory cleft*" OR "*anterior cranial fossa*"). The exclusion criteria were studies referring to other types of tumor (n = 19); GCTB involving locations such as the temporal, occipital, or mandibular bones (n = 50); studies lacking sufficient data (n = 3); studies describing cases already reported in prior studies (n = 3); and studies not published in English or French (n = 1). This review included studies published between 1982 and 2022, from which demographic data, tumor location, extension to the anterior skull base, type of primary surgery, recurrence rate, use of adjuvant treatment, and follow-up duration were collected. Additionally, we described a clinical case of GCTB managed at our institution using the endoscopic endonasal transcribriform approach.

Results

This systematic review identified 112 articles. After initial selection based on titles and abstracts, exclusion criteria were applied, yielding 36 studies for full-text analysis. Among these, 20 described cases of GCTB involving the anterior skull base, including a total of 21 patients (Table 1).

The average age of the patients was 21 years (σ = 9.8, range: 2–36 years), and 14 were female (67%). The primary tumor location was the sphenoid sinus/clivus in 17 cases (80.9%), the ethmoid sinus in 3 cases (14.3%), including one originating in the cribriform plate, and the frontal sinus in 1 case (4.8%). The most common symptoms were headache, reported by 16 patients (76.2%), followed by diplopia, reported by 10 (47.6%), and decreased visual acuity, also reported by 10 patients (47.6%).

Treatments involved an external approach in 11 cases (52.4%), endoscopic endonasal approach in 8 cases (38.1%), and combined approach in 1 case (4.8%). Complete tumor resection was achieved in 8 cases, while 11 cases were classified as incomplete or subtotal resections. Adjuvant treatments included radiotherapy, administered to 15 patients (71.4%) at doses of 40–60 Gy, and monoclonal antibody administration alone in 2 cases (9.5%). The mean follow-up period was 41.2 months. At the time of publication, 11 patients (52.4%) were disease-free, 7 patients (33.3%) had residual or recurrent disease, and 1 patient had died due to radiotherapy complications. Outcomes were not reported for 2 cases.

Illustrative case report:

We report the case of a 20-year-old woman with no notable medical history who

Table 1
Literature review of GCTB cases extending to the anterior skull base

Author	Sex/ age	Clinical presentation	Location	Primary treatment	Complete resection	Adjuvant therapy	Follow-up (months)	Outcome
Singh et al. 2020	F, 35	Headache, diplopia, visual impairment	Clivus	EE	No	RT, 60 Gy	6	Residual tumor
Pousti et al. 2020	F, 27	Headache, diplopia, visual impairment, nasal obstruction	Sphenoid	EE	No	Denosumab	18	Disease free
Biswas et al. 2018	F, 18	Headache, paresthesia V1	Sphenoid	External – craniotomy	No	RT, 45 Gy	N/A	Died due to RT complications
Sekar et al. 2018	M, 26	Headache, diplopia, paresis VI	Sphenoid	EE	Yes	Denosumab (neo)	14	Disease free
Satapathy et al. 2018	M, 24	Headache, diplopia, visual impairment, paresis VI	Clivus	External – craniotomy	Yes	RT, 60 Gy	8	Disease free
Tonari et al. 2017	F, 13	Visual impairment	Sphenoid	EE	No	RT	144	Residual tumor
Yildirim et al. 2014	F, 27	Headache, diplopia, paresis VI	Sphenoid	EE	Yes	RT, 50-60 GY	6	Disease free
Iacoangeli et al. 2013	M, 31	Headache, diplopia, paresis VI	Clivus	EE	Yes	-	72	Disease free
Roy et al. 2013	M, 19	Headache	Clivus	External – Le Fort 1	No	RT, 45 Gy	18	Residual tumor
Battoo et al. 2012	F, 34	Nasal obstruction, epistaxis	Ethmoid	N/D	Yes	RT, 52 Gy	36	Disease free
Kamoshima et al 2011	F, 2	Frontal swelling	Frontal	External – craniotomy	Yes	-	18	Disease free
Company et al. 2009	M, 19	VA decrease, exophthalmos	Sphenoid	External – craniotomy	N/A	-	N/A	Recurrence
Gupta et al. 2008	F, 17	Headache, diplopia, visual impairment	Clivus	External – Le Fort 1	No	RT, 45 Gy	24	Residual tumor
Noel et al. 2006	F, 29	Headache, diplopia, visual impairment	Sphenoid	EE	No	RT, 43 Gy	83	Residual tumor
Zorlu et al. 2006	F, 19	Headache, diplopia	Sphenoid	EE	No	RT, 60 Gy	16	Recurrence
Hub et al. 2002	F, 15	Headache, diplopia, paresis VI	Cribriform plate	External – craniotomy	No	RT 57 Gy (recurrence)	69	Disease free
Sharma et al. 2002	M, 36	Headache, amaurosis, nasal obstruction	Sphenoid	External – craniotomy	No	RT	120	Disease free
	M, 17	Headache, amaurosis, nasal obstruction	Sphenoid	Combined	No	RT	14	Disease free
Lewark et al. 2000	F, 11	N/A	Clivus	External – Le Fort 1	No	RT	N/A	N/A
Uttley et al. 1991	F, 27	Headache, visual impairment	Sphenoid	External – Le Fort 1	No	RT	N/A	N/A
Handler et al. 1982	F, 14	Headache, epistaxis	Ethmoid	External – craniotomy	No	-	24	Disease free

M – male, F – female, EE – endonasal endoscopy, N/A – not available, GCTB – giant cell tumor of bone, RT –radiotherapy, VA – visual acuity

presented with frontal headache. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a well-defined globular lesion measuring 37 x 32 x 18 mm in its largest axis, centered on the cribriform plate, accompanied by bone erosion, and extending to the olfactory and ethmoid grooves (Figure 1). No evidence of intracranial extension was found. A biopsy confirmed the diagnosis of GCTB. Bone scintigraphy and laboratory tests excluded secondary lesions and hyperparathyroidism.

Figure 1
A. Preoperative computed tomography (CT); B. Surgical field after removal of the cribriform plate and exposure of the dura; C. Defect reconstruction 6 months postoperatively; D. CT and magnetic resonance imaging (T2) 6 months postoperatively showing no recurrence

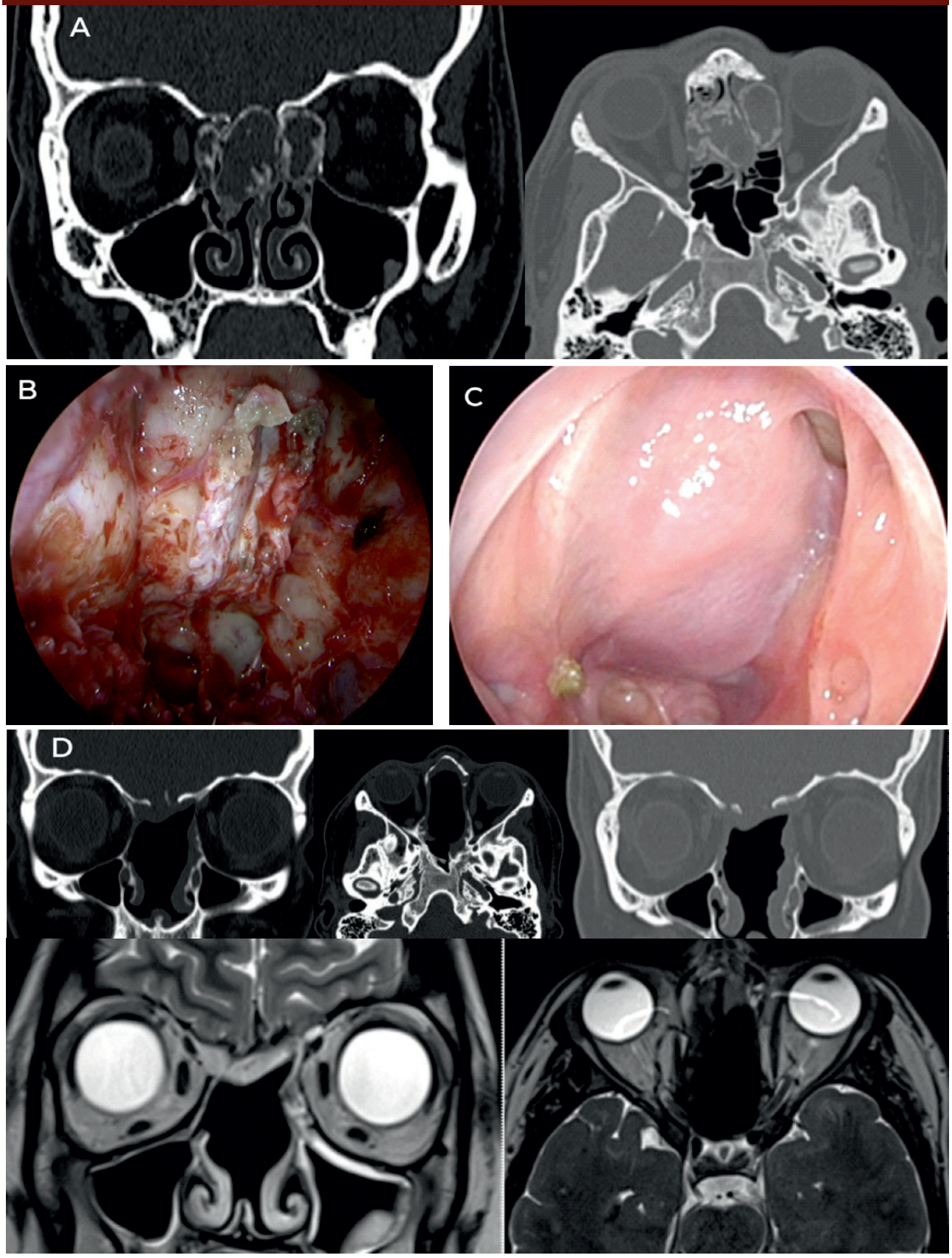
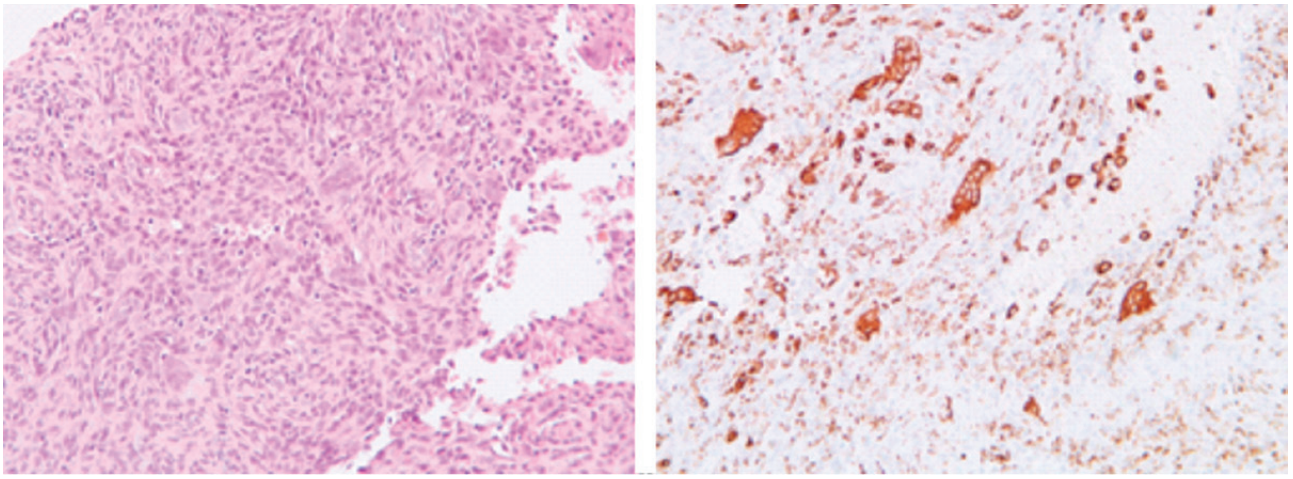


Figure 2
Osteoclastic multinucleated giant cells and mononucleated cells (A), which are immunoreactive for CD68 (B). No mitoses or necrosis are observed



Complete resection of the tumor, which involved the dural region of the anterior cranial fossa superiorly and the orbits laterally, was achieved via the endoscopic endonasal transcribriform approach. Dural integrity was preserved, and there were no perioperative complications.

The defect was reconstructed using a vascularized nasoseptal flap that extended to the nasal floor and lateral nasal wall. Histopathological examination confirmed the diagnosis, revealing rare mitoses without evidence of atypia or necrosis (Figure **2**). The patient has been followed up for eight months without complications, apart from the expected hyposmia.

Discussion

The literature on GCTB involving the anterior skull base is limited and predominantly comprises case reports. This systematic review identified 22 cases of GCTB involving the anterior skull base reported since 1982, including the case described in this study, which prompted this review. Zhang et al. demonstrated statistically significant differences in the distribution of GCTB in the skull. The sphenoid (54%) and temporal (37%) bones, formed by endochondral ossification, are the most frequently affected sites, followed by the occipital (5%) and frontal (3%) bones.[3,11]

GCTB at the skull base and paranasal sinuses presents additional management challenges due to its high recurrence rate, which varies between 7–70% depending on the extent of resection, its potential for locally aggressive behavior, and proximity to vital structures that often hinder complete resection.[5,12]

On imaging, GCTB typically presents as an expansile lesion with contrast enhancement due to its vascular nature, along with occasional lytic bone lesions visible on radiographs and CT scans. On MRI, GCTB commonly appears isointense on T1-weighted images and hypointense on T2-weighted images. This imaging modality also facilitates the assessment of tumor extension or involvement of soft tissues or adjacent structures, including the dura, orbits, or neurovascular components.[7,13,14] The differential diagnoses of GCTB include giant cell granuloma, brown tumor associated with hyperparathyroidism, chordoma, aneurysmal bone cyst, fibrous dysplasia, eosinophilic granuloma, and plasmacytoma. A definitive diagnosis requires histopathological examination, as imaging findings are non-specific.[7,13–15]

The receptor activator of nuclear factor kappa-B (RANK) signaling pathway plays a crucial role in bone remodeling by ensuring a physiological balance between bone formation and absorption. In GCTB, this

pathway is deregulated by the overexpression of RANK ligand (RANKL), produced by tumor stromal cells. This activates RANK in osteoclast-like giant cells, stimulating their differentiation and activation, thereby promoting bone resorption and tumor growth.[12,16] Chromosomal instability secondary to centrosome changes is a potential mechanism underlying the aggressive nature of GCTB.[16] Histologically, GCTB consists of osteoclast-like multinucleated giant cells, round monocyte-like mononuclear cells, and neoplastic spindle-shaped stromal fibroblast-like cells.

Given that only a few cases of GCTB involving the skull are described in the literature, together with its unpredictable clinical behavior and variable therapeutic outcome, no guidelines on the treatment of GCTB currently exist. According to previous studies, surgical excision remains the treatment of choice, with complete resection achieving local control rates between 85–90%.[3,12,14,16–18] In the six cases in this review where complete resection was achieved, the status outcome was "disease-free", with three of them undergoing adjuvant radiotherapy and one receiving neoadjuvant treatment with denosumab.

The endoscopic endonasal approach provides a less invasive route for accessing the anterior skull base compared to the external approach, and enables precise and effective tumor identification and resection with reduced morbidity.[18,19]

However, achieving complete resection with clear margins is crucial, although this is often hindered by the tumor's anatomical location or involvement of vital structures. Therefore, adjuvant treatment is frequently employed, particularly when complete resection is not feasible.[13,16] In the reported case, the use of a vascularized pedicled nasal flap enabled rapid mucosal healing of the final bone defect, ensuring effective reconstruction and reducing the risk of postoperative complications such as cerebrospinal fluid fistula. Follow-up with imaging and endoscopic evaluations are essential to monitor for potential recurrences, particularly in cases involving grafts or intranasal pedicled flaps.

Although GCTB was previously considered radioresistant with a potential for sarcomatous transformation following radiotherapy, recent advancements in radiotherapy techniques have yielded encouraging results. Studies have reported five-year local control rates of 70–85% with doses of 45–55 Gy for postoperative adjuvant treatment. Furthermore, long-term studies have not identified an increased rate of malignant transformation.[13,14]

Radiotherapy, either adjuvant or isolated, has been shown to positively impact disease-free survival, enhancing local control in cases of incomplete resection, recurrence, or where surgery is not feasible.[16,17]

Denosumab, a human monoclonal antibody targeting RANKL, was initially indicated for osteoporosis to prevent bone resorption. Approved in 2013 by the European Medicines Agency and US Federal and Drug Administration (FDA) for the treatment of unresectable or metastatic GCTB, as well as recurrent or progressive cases, it is administered at a dose of 120 mg subcutaneously once a week for three weeks, followed by monthly doses. Denosumab inhibits osteoclastic activity and reportedly achieved a tumor burden reduction of approximately 90%. This new therapeutic option is particularly valuable in cases of incomplete resection and as a neoadjuvant to facilitate cytoreduction of previously unresectable tumors, as described by Sekar et al. However, the efficacy, dose, and treatment duration of immunotherapy for skull bone tumors remain unknown and it may lead to adverse effects, such as hypercalcemia, stress fractures, and osteonecrosis.[12,16,20]

No predictive factors for progression of GCTB have been identified, highlighting the importance of regular long-term follow-up. While most recurrences occur within the first two years, late recurrences, including malignant transformation, have been reported even after 10 years of follow-up.[21]

Conclusion

Based on the results of the literature review, nasal and sinus GCTB involving the anterior skull base are extremely rare, with our case being only the second reported case to originate from the cribriform plate. Despite being benign, the tumor exhibited aggressive behavior. Complete surgical excision using the endoscopic endonasal approach was successfully achieved without complications.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

The authors declare that they have obtained signed consent from the participants and that they have local ethical approval to carry out this work.

Financial support

This work did not receive any grant contribution, funding or scholarship.

Scientific data availability

There are no publicly available datasets related to this work.

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