

Sinonasal giant cell tumour. Report of four cases and review of the literature

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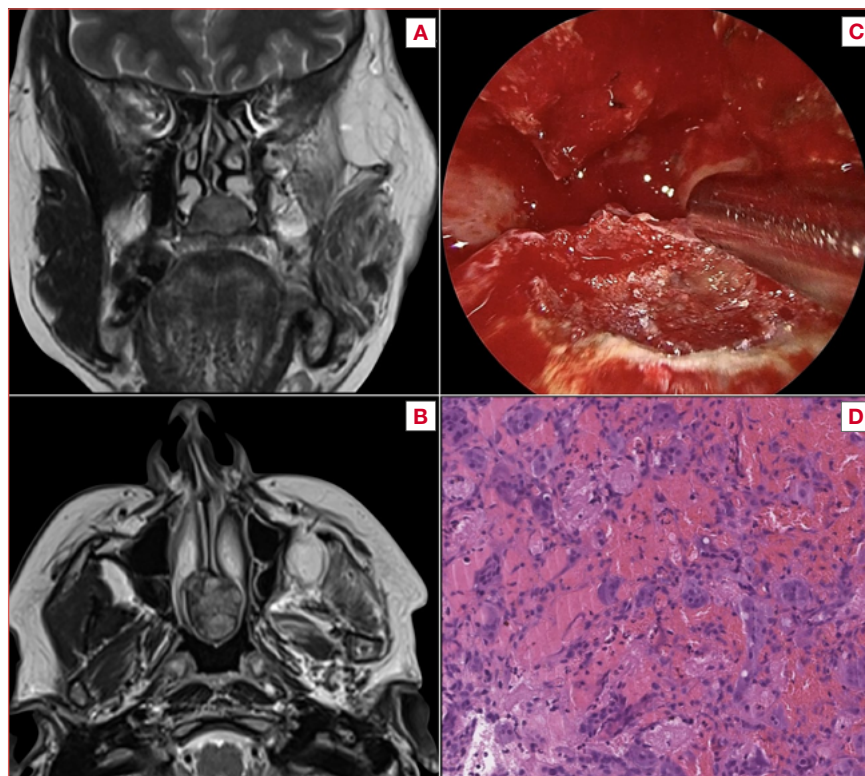
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Cover figure. Case 2 from the present series. **A-B)** Contrast-enhanced MRI T2-weighted sequences showing the lesion centred on the nasal rostrum in coronal (**A**) and axial (**B**) view. **C)** An intraoperative detail during the endoscopic resection revealing the base of implant of the lesion. **D)** Haematoxylin and eosin stains showing non-capsulated proliferation of spindle-shaped elements with multinucleated osteoclast-like giant cells, incorporating bone tissue.

Summary

Objective. Sinonasal giant cell tumour (SnGCT) is very rarely reported. The aim of the study is to present a series of SnGCT treated with an endoscopic or combined approach and to carry out a review of the literature on this topic.

Methods. This case series encompassed the clinical data of all the SnGCT surgically treated with curative intent at two different referral centres, between 2001 and 2024. The information was extrapolated to report epidemiologic and clinical data, surgical approach and follow up. A comprehensive clinical review of the literature was also carried out.

Results. Among 4 patients included, 3 were treated with a pure endoscopic resection and remained disease-free at the last follow up, while one was managed with a combined approach, who is alive with disease. From the review we found only 32 cases of SnGCT reported, mostly treated with an open approach. Local recurrence was documented in 12.5% of cases, while distant metastasis in 3%.

Conclusions. SnGTC is a benign but locally aggressive neoplasm that can present as a lytic lesion.

The clinical behaviour of GCT is unpredictable, and it tends to recur locally and may even metastasise. In the nose and paranasal sinuses it is an exceedingly rare entity, but should be considered in the differential diagnosis with a large variety of histologies. Surgery is the treatment of choice for resectable lesions.

Keywords: rare tumours, endoscopic sinus surgery, giant cell tumour, sinonasal neoplasm, review

Introduction

Sinonasal giant cell tumour (SnGCT) is a benign primary tumour of the bone that represents up to 5% of skeletal neoplasia¹⁻³. It is most commonly reported in adults, typically affecting the epiphysis of long bones, such as distal femur and proximal tibia, and is slightly more common in females⁴. This type of bone tumour is exceedingly rare in head and neck region, accounting for about 2% of all GCT, the majority found in the sphenoid, ethmoid, and temporal bones⁵. Nevertheless, it presents certain features that make it relevant in the differential diagnosis of sinonasal masses. Indeed, SnGCT can be misdiagnosed both as fibro-osseous lesions and hypervascularised neoplasms, with biopsy often contraindicated. Moreover, it can be locally aggressive, leading to cortical bone destruction^{6,7}, with eventually recurrence⁸, and some reported cases of malignant transformation and distant metastases⁹. In the present paper we report 4 cases of SnGCT treated via pure endoscopic or endoscopic-assisted resection. A review of the literature on this topic was also carried out.

Materials and methods

The current study is a retrospective analysis of primary SnGCT in patients admitted and treated with curative intent at the Unit of Otorhinolaryngology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, and the Unit of Otorhinolaryngology, ASST Spedali Civili di Brescia, Brescia, Italy, from 2001 to 2024. The work up of the patients consisted in radiological imaging with cone beam computed tomography (CBCT) and contrasted enhanced magnetic resonance imaging (MRI). Definitive pathologic diagnosis was established by consistent histology and immunohistochemistry. The information was extrapolated to report epidemiologic and clinical data, surgical approach and follow-up.

A comprehensive clinical review of the literature was also carried out on Scopus, PubMed/MEDLINE, Cochrane Library, Embase, ResearchGate and Google Scholar databases using relevant keywords, phrases, and MeSH terms. An example of a search strategy was the one used for PubMed/MEDLINE: “giant cell tumour” [All Fields] AND (nasal sinuses [MeSH Term] OR nasal fossa [MeSH Terms] OR surgery, endoscopic surgery [MeSH Terms]). References were scrutinised for additional articles.

Results

In the series were included 4 cases of SnGCT surgically treated with curative intent in the 2 referral centres.

Case presentation

CASE 1

A 12-year-old girl presented with bilateral worsening nasal obstruction lasting a few months. The patient had a family history of cherubism. The endoscopic examination showed a submucosal regular lesion centred on the lower third of the nasal septum, with the root on the nasal floor. The patient was studied with CBCT followed by a contrast enhanced MRI. The biopsy was avoided because the lesion appeared hypervascularised. An expert radiologist hypothesised the benign nature of the lesion, and the possible consistency with SnGCT, also considering the family history of the patient. A complete resection was obtained via pure endoscopic transnasal surgery. The definitive histological diagnosis was consistent with SnGCT. The histopathological analysis with routine haematoxylin and eosin staining revealed spindle-shaped elements with numerous multinucleated osteoclast-like giant cells, with haemosiderin pigment and haemorrhage, incorporating bone tissue. Immunohistochemical studies were performed with appropriate positive and negative controls. The giant cells were strongly positive for macrophage marker CD68. There was no major bleeding or postoperative haemorrhagic complications. At 6-year follow-up the patient resulted free of disease. Radiology and histology of the patient are reported in Figure 1.

CASE 2

A 45-year-old woman in follow-up with a previous history of a surgically treated GCT of the mandible, had a radiological finding of nasal mass at the contrast-enhanced MRI. She therefore completed the work up with a CBCT and an endoscopic examination: in consideration of the previous medical history, the tumour was classified as a SnGCT of the nasal rostrum with a large root on the nasal floor. The periphery of the lesion appeared hyperostotic, and thus a preoperative biopsy was avoided. The resection of the tumour was completed with a pure endoscopic transnasal approach, with posterior septectomy, and drilling of the basement of the tumour on the nasal floor. The definitive histologic diagnosis was consistent with GCT. The histopathological anal-

ysis with routine haematoxylin and eosin stains revealed non-capsulated proliferation of spindle-shaped elements with numerous multinucleated osteoclast-like giant cells, with haemosiderin pigment and haemorrhage, incorporating bone tissue. Immunohistochemical studies were performed with appropriate positive and negative controls. The giant cells were strongly positive for macrophage marker CD68. The patient is free of disease after 4 years of follow-up. Radiological, clinical and histological images of the patient are shown in the Cover figure.

CASE 3

An 18-year-old male patient presented with bilateral nasal obstruction persisting for 2 months. He had undergone surgery for nasal polyposis elsewhere 2 years earlier; histopathological report was not retrieved. Contrast-enhanced MRI revealed a 4 cm lesion originating from the posterior nasal septum, obstructing the nasal cavities. A biopsy was consistent with SnGCT, and an endoscopic transnasal resection with septectomy was carried out. The final diagnosis confirmed a SnGCT of the nasal rostrum. Histopathology showed spindle-shaped elements with numerous multinucleated osteoclast-like giant cells, haemosiderin pigment, haemorrhage, and bone tissue incorporation. Immunohistochemistry revealed PGM-1 and CD1673 positivity in giant cells, partial smooth muscle actin positivity in spindle cells, and negative S100 protein. Postoperative course was uneventful. At the 2-year follow-up, the patient remained disease-free.

CASE 4

A 70-year-old woman with Paget's disease was referred for recurrent SnGCT. Primary disease was located in the right maxillary sinus; during follow up, MRI diagnosed a mass in the right nasal fossa suspicious for disease relapse. She underwent centripetal subperiosteal endoscopic resection of the right nasal fossa, including medial maxillectomy, maxillary mucosa and bony roof, ethmoidectomy (including lamina papiracea), lacrimal pathway, and pterygopalatine fossa content. Histology confirmed the diagnosis of SnGCT with numerous multinucleated osteoclastic giant cells and mononucleated fibro-histiocytic cells, along with sclerosis, haemosiderin deposits, and xanthomatous histiocytes. Adjacent bone tissue alterations were consistent with Paget's disease.

During follow-up, several recurrences occurred. At 2 months, a lesion consistent with SnGCT was removed at the occipital bone. Then, 2 years later the disease relapsed at both right maxillary and occipital sites. The maxillary recurrence was managed with an endoscopic approach requir-

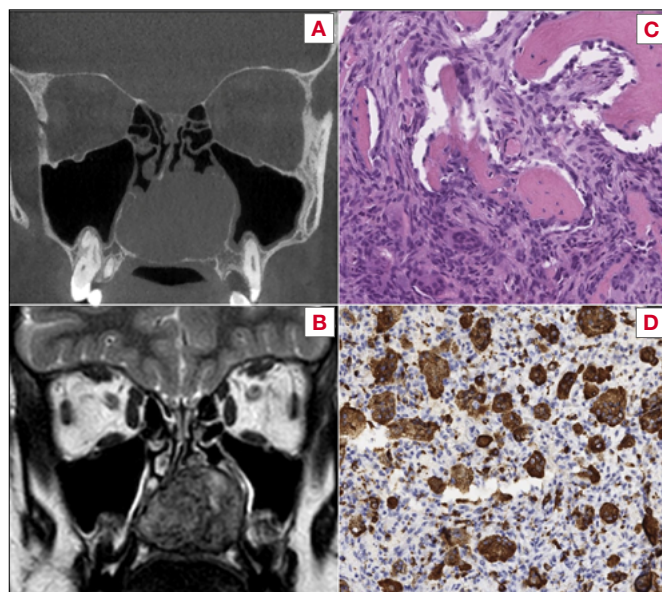


Figure 1. Case 1 from the series. **A)** CBCT coronal view showing a soft tissue density expansive mass with destructive progression into the palate; **B)** Contrast-enhanced MRI T2-weighted coronal sequence showing the hypervascularity of the lesion; **C)** Haematoxylin and eosin stains showing spindle-shaped elements with numerous multinucleated osteoclast-like giant cells, with haemosiderin pigment and haemorrhage, incorporating bone tissue; **D)** Immunohistochemistry: the giant cells were strongly positive for macrophage marker CD68.

ing resection of the periorbita and the ethmoid roof. One year later, SnGCT recurred in the left nasal fossa requiring endoscopic centripetal resection with ethmoidectomy and medial maxillectomy.

In view of the concomitant Paget disease (a risk factor for SnGCT), it was impossible to assess whether the localisations at occipital site and left nasal fossa were metastatic disease or second primaries. The last MRI (2 years after the last procedure) showed a 17 mm solid mass in the left nasal fossa extending from the orbital floor to the nasal cavity roof, displacing the superior turbinate with possible intraorbital extension. A 4 cm mass infiltrated the left retroauricular and nuchal soft tissues, destroying the outer diploe at the temporo-occipital junction. The hard palate lesion extended beyond the midline, lifting the nasal cavity floor mucosa and involving the lower nasal septum. The patient refused further surgical treatment and was lost at follow-up.

The patients' data are summarised in Table I.

The patient and the legal guardians of Case 1 agreed to the publication of the clinical data.

Literature search and results

A total of 25 studies with 32 patients were included in this

Table I. Cases presented.

Patient	Age (years)	Gender	Site of tumor	Type of surgery	State	Follow-up (months)
1#	12	Female	Nasal cavity	Pure endoscopic	NED	74
2#	45	Female	Nasal cavity	Pure endoscopic	NED	48
3#	18	Male	Nasal cavity	Pure endoscopic	NED	24
4#	70	Female	Multiple	Endoscopic-assisted	AWD	96 (LAF)

NED: no evidence of disease; AWD: alive with disease; LAF: lost at follow-up.

review (Tab. II). The male to female ratio was 0.37. Ten (31%) patients presented SnGCT with multiple locations, 9 (28%) presented a sphenoid sinus involvement, 4 (12.5%) maxillary sinus, 5 (15.6%) nasal cavities, 3 (9.3%) frontal sinus, and 1 (3%) ethmoid. Most patients (53%) underwent exclusive surgical resection, although only 4 (12.5%) were treated with pure endoscopic surgery, while 47% of cases integrated surgery with adjuvant denosumab or radiation therapy. Local recurrence was documented in 12.5% of cases, while distant metastasis in 3%. In particular, 79% of pure surgical excisions obtained free margins of resection (R0) and none had local recurrence. On the other hand, the patients who underwent multimodal treatment had positive margins (R1 or R2) in 70% of cases and 33% of these had local recurrence.

Discussion

Differential diagnosis of sinonasal benign and indolent tumours continues to be demanding in consideration of the large variety of histologies. However, it is well known that benign masses are commonly included in 3 main groups: hypervascularised malformations as the juvenile angiofibroma, fibro-osseous lesions, and sinonasal papillomas. To these, several types of mesenchymal locally aggressive tumours, such as desmoid type fibromatosis, solitary fibrous tumour, and sinonasal glomangiopericytoma must be added. When a tumour falls outside these groups, the diagnosis can be very challenging, and integration between familiar and medical history, and radiology becomes essential. GCT is a benign primary tumour of the bone, extremely rare in the sinonasal district, accounting for less than 2% of all GCTs, the majority reported in multiple sites. However, it has some peculiarities that make it of interest in the differential diagnosis of sinonasal masses. Indeed, SnGCT can be misdiagnosed as fibro-osseous lesions, hypervascularised neoplasms, or other borderline mesenchymal tumours. Most of the available literature about this entity in the sinonasal region consists of case reports. During our search,

only 32 reported cases of SnGCT were found (Tab. II). Because of the very indolent symptoms, these tumours can be diagnosed at an advanced stage, which can affect the choice of the treatment since surgery can have a non-deniable rate of complications and cosmetic impact.

Clinical and radiological work up

Symptoms like nasal obstruction, frequent nasal infection and epistaxis are associated with multiple conditions of nasal and paranasal sinuses. Radiologic findings in SnGCT are characterised by varying degrees of bone destruction and these lesions tend to be locally aggressive¹⁰. CBCT/CT and MRI are considered the ideal tools to characterise and diagnose SnGCT. On CBCT/CT, this type of tumour often appears as a soft tissue density mass with destructive expansion into the bone, without cortex involvement¹¹. MRI provides better characterisation of the lesion through its higher contrast resolution and multiple sequences¹¹. SnGCT usually demonstrates low to intermediate signal intensity on T1 sequencing, hypointensity on T2 and enhance with gadolinium¹².

The diagnosis is most frequently obtained postoperatively because a pretreatment biopsy may be difficult in view of hypervascularity, site, or ossification of the lesion¹³. Nevertheless, if the lesion is easily accessible, it is often preferable to perform a preoperative biopsy (Case 3).

Histologic features

The histological appearance of SnGCT consists in numerous large multinucleated giant cells dispersed in a background stroma of mononuclear spindle cells and monocytes. The monocyte nuclei have features identical to those of the larger osteoclast-like giant cells, which can contain large number of these nuclei (> 50). However, the histological pattern can vary and can contain areas of cystic degeneration, haemorrhage, haemosiderin deposition, occasional mitotic figures, or increased spindle cell stroma. Various conditions show multinucleated osteoclast-like giant cells in a background of oval to spindle-shaped mononuclear

Table II. Review of the literature.

Study	Year	Study design	Patients	Gender	Site	Treatment	Margins	Reoccurrence	Metastasis
Peimer ²⁶	1954	Case series	1#	M	Maxillary sinus	Open surgery	R0	No	No
			2#	M	Multiple sites	Open + adjuvant therapy	R2	No	No
Burnam ²⁷	1970	Case report	1#	F	Multiple sites	Open surgery	R0	No	No
Sgouras ²⁸	1971	Case report	1#	M	Nasal cavity	Open surgery	NS	No	No
Fu ¹⁰	1974	Case series	1#	F	Maxillary sinus	Open surgery	R0	No	No
			2#	F	Maxillary sinus	Open surgery	R0	No	No
			3#	F	Frontal sinus	Open surgery	R0	No	No
			4#	M	Multiple sites	Open surgery	R2	Yes	No
Hlaváček ²⁹	1974	Case series	1#	F	Frontal sinus	Open surgery	R0	No	No
			2#	M	Multiple sites	Open surgery	R0	No	No
Handler ³⁰	1982	Case report	1#	F	Multiple sites	Open surgery	R0	No	No
Wolfe ³¹	1983	Case series	1#	F	Sphenoid sinus	Pure endoscopic + adjuvant therapy	R0	No	No
			2#	F	Multiple sites	Open + adjuvant therapy	R0	No	No
			3#	M	Sphenoid sinus	Pure endoscopic + adjuvant therapy	R0	No	No
Anand ³²	2001	Case report	1#	M	Nasal cavity	Open surgery	R0	No	No
Chan ³³	2003	Case report	1#	M	Multiple sites	Pure endoscopic	R0	No	No
McKinney ³⁴	2005	Case report	1#	F	Sphenoid sinus	Open surgery	R2	Yes	Yes
Tuluc ³⁵	2006	Case report	1#	F	Nasal cavity	Pure endoscopic	R0	No	No
Esposito ³⁶	2006	Case report	1#	F	Sphenoid sinus	Pure endoscopic + adjuvant therapy	R2	No	No
Company ³⁷	2009	Case report	1#	M	Sphenoid sinus	Open surgery	R2	Yes	No
Battoo ³⁸	2010	Case report	1#	F	Sphenoid sinus	Open + adjuvant therapy	R1	No	No
Huang ³⁹	2013	Case report	1#	F	Sphenoid sinus	Pure endoscopic	R0	No	No
Goto ⁴⁰	2016	Case report	1#	M	Sphenoid sinus	Pure endoscopic + adjuvant therapy	R2	No	No
Rodriguez ⁴¹	2017	Case report	1#	F	Frontal sinus	Open surgery	R0	No	No

Table II. *continues.*

Study	Year	Study design	Patients	Gender	Site	Treatment	Margins	Reoccurrence	Metastasis
Tonari ⁴²	2017	Case report	1#	F	Multiple sites	Pure endoscopic + adjuvant therapy	R2	Yes	No
Yip ⁴³	2018	Case report	1#	F	Ethmoid sinus	Open + adjuvant therapy	R1	No	No
Rosa ⁴⁴	2018	Case report	1#	M	Maxillary sinus	Open + adjuvant therapy	R2	Yes	No
Pousti ⁴⁵	2020	Case report	1#	F	Multiple sites	Pure endoscopic + adjuvant therapy	R2	No	No
Aassouani ⁴⁶	2022	Case report	1#	F	Multiple sites	Pure endoscopic + adjuvant therapy	NS	No	No
Hu ⁴⁷	2022	Case report	1#	M	Sphenoid sinus	Pure endoscopic	R2	No	No
Serafini ⁴⁸	2023	Case report	1#	F	Nasal cavity	Pure endoscopic	R0	No	No
Linxweiler ⁴⁹	2024	Case report	1#	F	Nasal cavity	Pure endoscopic	R0	No	No

M: male, F: female, NS: non specified.

cells. These include giant cell granulomas (GCGs), brown tumour of hyperparathyroidism and cherubism. The differential diagnosis between GCTs and GCGs is usually guided by symptomatology (reported in 72% of GCTs while only 15% of GCGs) and the distribution pattern of giant cells in the stroma (homogeneously dispersed in 80% of GCTs versus grouped in clusters in 86.7% of GCGs). The most important difference between these lesions is the prognosis, GCTs being more aggressive and with a higher risk of recurrence ^{6,12}. Moreover, the gene mutated in cherubism has been mapped to chromosome 4p16.3 ¹⁴. Missense mutations are observed in the *SH3BP2* gene mainly clustered in exon 9 ^{15,16}. Recently, a somatic mutation of this gene was described in a case of GCT ¹⁷.

Treatment

An endoscopic endonasal approach should be preferred when feasible. In fact, for both benign and malignant sinonasal tumours, the endoscopic approach is considered the gold standard of treatment, as it allows for radical resection even in cases of locally advanced disease and reduces the complications associated with open approaches. In selected cases, the resection must be integrated with an open approach ¹⁸. The resection of SnGCT can be compared to that of other fibro-osseous lesions of the sinonasal

region. The pathological tissue needs to be excised taking into consideration the morbidity of the procedure. In some extended cases involving noble structures a planned R2 excision could be necessary. In cases of complete tumour removal, adjuvant radiation therapy is not indicated ¹⁹. On the other hand, in case of involvement of vital structures, a planned R2 resection can be unavoidable. If total tumour excision is not obtainable, subtotal excision plus radiotherapy results in acceptable tumour control rates. For many years pharmacological therapy was not considered in the treatment of SnGCT ¹⁹. However, knowing that giant cells in SnGCT overexpress the receptor activator of nuclear factor kappa- β ligand (RANKL) ^{20,21} has led to the clinical application of denosumab, a human monoclonal antibody that reduces osteolysis, inhibiting RANKL. This treatment is mostly utilised in patients with unresectable or metastatic disease, as it reduces tumour burden, improves symptoms, and helps prevent tumour recurrence. A series of clinical trials and case reports have shown that denosumab can control the disease and reduce the extension of surgery in patients with GCT ²². In a neoadjuvant setting, it may promote *en bloc* resection because of the development of a calcified rim around the tumour and its soft tissue component. However, in these studies the median follow-up was roughly one year, which is too short

to demonstrate efficacy and safety in complicated cases. Recent studies reported a higher local recurrence rate in patients treated with neoadjuvant denosumab, possibly because of more limited surgical resections²³⁻²⁵.

Conclusions

SnGCT is a benign but locally active or aggressive bone neoplasm that typically presents as a lytic lesion. The clinical behaviour of GCT is unpredictable, and it tends to recur locally and even metastasise. In the nose and paranasal sinuses it is an exceedingly rare entity, but it should be considered in the differential diagnosis with a large variety of histologies, such as fibro-osseous lesions, hypervascularised masses, and locally invasive mesenchymal tumours. Surgery is treatment of choice for resectable lesions, with endoscopic transnasal surgery being first-line whenever feasible. The use of the monoclonal antibody denosumab is an option in selected cases (large masses, recurrence non amenable to surgery, unfit patients for surgery); however, larger trials are needed to evaluate the risks and benefits of this treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AC, RA: study concepts; RA, DM: study design; AC, FDP, CLM: data acquisition; AB, RA, AC, DM: quality control of data and algorithm; AC, CLM, DM: data analysis and interpretation; AC, RA, DM: manuscript preparation; DM, RA, AB, HI: manuscript editing; CP, AGD, LC, DM, RA: manuscript review.

Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All authors have read and approved the manuscript.

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