Clinical Case Report

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Clinical characteristics and management of primary granulocytic sarcoma of the oral cavity

A case report and literature review

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Abstract

Introduction: Granulocytic sarcoma (GS) is a commonly occurring tumor comprising immature myeloid cells, which are usually related to acute or chronic myelocytic leukemia. The tumor rarely precedes leukemia without bone marrow involvement and is called primary GS. Although primary GS can occur in any body part, the involvement of the oral cavity is uncommon.

Patient concerns: A 49-year-old woman hospitalized at the Department of Plastic and Maxillofacial Surgery presented with a growing mass in her left maxillary hard palate dating two months back. No obvious physical findings were noted during general examination. She was diagnosed with an oral ulcer at a local clinic, and received antibiotics. However, the symptoms did not improve; the mass became bigger and painful.

Diagnosis: An incisional biopsy of the oral mass was performed, the immunohistochemistry showed that the tumor cells tested positive for myeloperoxidase, CD4, BCL-2, KI-67. Bone marrow aspiration was negative for malignant cells, and the laboratory test results revealed only monocytosis. Standard bone marrow cytogenetic analysis showed a normal karyotype and leukemia-related fusion gene detection was normal. Therefore, the final diagnosis was intraoral primary GS.

Interventions: The patient was treated with a chemotherapy regimen based on idarubicin and cytarabine arabinoside.

Outcomes: After 2 cycles of idarubicin and cytarabine arabinoside regimen chemotherapy, the patient achieved complete remission. The tumor was barely visible in the left maxillary hard palate. There has been no evidence of disease spread and progression after 1 year of follow-up.

Conclusions: Careful morphological and immunohistochemical analyses, correlating with clinical data are necessary to establish the diagnosis of oral primary GS. Early aggressive systemic chemotherapy can effectively relieve symptoms, significantly reducing primary GS conversion into acute myelocytic leukemia and prolonging overall survival.

Abbreviations: AML = acute myelocytic leukemia, BMT = bone marrow transplantation, GS = granulocytic sarcoma, HSCT = hematopoietic stem cell transplantation, IHC = immunohistochemistry, MPO = myeloperoxidase, MS = myeloid sarcoma.

Keywords: primary granulocytic sarcoma, oral tumor, clinical characteristics

1. Introduction

Granulocytic sarcoma (GS) is a malignant tumor derived from the bone marrow and located outside the bone marrow. The tumor is also called chloroma, extramedullary myeloid tumor, or myeloid sarcoma (MS), which generally presents with a green color due to the presence of myeloperoxidase (MPO).[1–2] GS usually occurs with acute myelocytic leukemia (AML), myelodysplastic syndrome, myeloproliferative neoplasm or as a recurrence of AML. In majority of conditions, it occurs after the onset of leukemia. When it precedes leukemia without any apparent symptoms, it is termed as the primary or isolated type. It is reported that the ratio of primary GS reaches about 0.85% to 2.2% in patients with AML. It has a high risk of progression to AML within months or years.[3–5] GS can be found in any part of the body but more predominantly in the skin, soft tissues, and lymph nodes. Oral cavity GS rarely occurs, and the clinical characteristics are varied and usually atypical.[6,7] Therefore, it is crucial for oral clinicians to be able to accurately diagnose GS, which ensures prompt treatment to control the disease progression and reach a stable remission period.

Here, a rare case of primary GS is reported, presenting with intraoral involvement, including the mucosa of the left maxillary hard palate, and the adjoining edentulous region. Relevant literature was also reviewed to provide clinicians with additional clarifications on the clinicopathologic manifestation, differential diagnosis, treatment regimens, and prognosis of primary GS of the oral cavity.

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The patient has provided informed consent for publication of the case.

The datasets generated during and/or analyzed during the current study are publicly available.

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2. Case report

A 49-year-old woman hospitalized at the Department of Plastic and Maxillofacial Surgery, presented with a growing mass in her left maxillary hard palate dating 2 months back. She was diagnosed with an oral ulcer at a local clinic, and received antibiotics. However, the symptoms did not improve; the mass became bigger and painful. Her past medical history was unremarkable without any systemic disease. No obvious physical findings were noted during general examination. She had no bouts of fever, chills, night sweats, vomiting, or weight loss. The intraoral examination revealed that there was a mass measuring 3.0 cm × 2.0 cm in size, with ulcerated surface mucosa in the left maxillary hard palate (Fig. 1).

To obtain a definitive diagnosis, an incisional biopsy of the oral mass was performed under local anesthesia. Histologic examination using hematoxylin and eosin staining revealed that there was diffuse cell infiltration growth. Most cells were large, with vacuolated nuclei, obvious nucleoli and a basophilic cytoplasm containing granules (Fig. 2). For the final diagnosis, immunohistochemistry (IHC) was performed, and the tumor cells tested positive for MPO, CD4, BCL-2, KI-67 (Fig. 3), and CD117 and negative for CD3, CD5, CD20, CD56, bcl-6, Mum-1, CD123, MUM-1, TdT, Syn, SOX11, and C-myc. These results supported the diagnosis of GS.

The patient was then referred to the Hematology Department. Bone marrow aspiration was negative for malignant cells, and the laboratory test results revealed only monocytosis. Standard bone marrow cytogenetic analysis showed a normal karyotype and leukemia-related fusion gene detection was normal. Therefore, according to IHC and bone marrow aspiration results in combination with morphological features, the final diagnosis was intraoral primary GS.

A chemotherapy regimen comprising idarubicin 8 mg VD d_{1-3} and cytarabine arabinoside 150 mg VD d_{1-7} idarubicin and cytarabine arabinoside was initiated. During chemotherapy, the patient only appeared mild nausea, vomiting and canker sores (grade II). These symptoms gradually eased without special therapy. After 2 cycles of idarubicin and cytarabine arabinoside regimen chemotherapy, the patient achieved complete remission. The tumor was barely visible in the left maxillary hard palate (Fig. 4). The patient denied consolidation therapy or bone marrow transplant. Nevertheless, there has been no evidence of disease spread and progression after 1 year of follow-up.

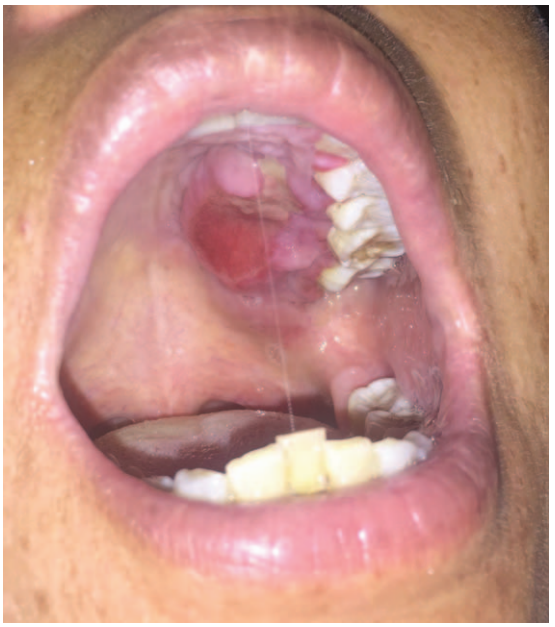

Figure 1. Interoral view a mass in the left maxillary hard palate with ulcerated surface mucosa.

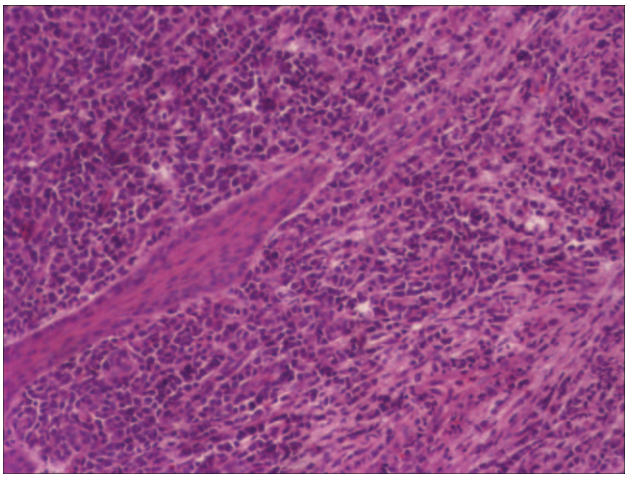

Figure 2. Histologic examination using hematoxylin-eosin (H&E) staining demonstrated that the cell diffuse infiltration growth, most cells were large, the nucleus was vacuolated, the nucleoli were obvious with basophilic cytoplasm containing granules. (magnifification: ×400).

3. Discussion

GS is an extramedullary solid tumor composed of immature myeloid cells. First described by Burns in 1811, then in 1853, King named GS as "chloroma," due to its green colored appearance when exposed to air, resulting from the presence of myeloperoxidase in the tumor cells. In 1966, Rappaport formally proposed the concept of GS. The classification includes non-leukemic GS (isolated or primary GS) and leukemic GS (extramedullary infiltration of leukemia).[8,9]

Primary GS occurs in approximately 2 per million persons. The oral cavity occurrence of primary GS is extremely rare. The clinical characteristics of oral primary GS are variable and usually nonspecific.[10] It is a challenge to diagnose oral primary GS based on symptoms and through routine examination. To improve the awareness of the disease, we retrospectively analyzed all cases of oral primary GS, which the tumor precedes leukemia without bone marrow involvement. There are only 31 cases published in PubMed literature together with our case (Table 1).[11–41] The average age of the patients was 44 years (ranging from 2 to 89 years), with a predilection for females (2:1). The tumor was mostly isolated. Commonly involved sites were the gingiva (40.6%), mandible (21.9%), and hard palate (15.6%). Only a few involved the lip, buccal mucosa, and multiple sites. The most common clinical feature of oral primary GS is a painful swelling or a nodule with a reddish to brownish ulcerated surface. In addition, imaging changes that present as soft tissue-occupying lesions, with or without bone erosions, are atypical.[42–43] Therefore, it is usually misdiagnosed as a dental ulcer, epulis and gingival hyperplasia, as well as malignant neoplasms. The challenge to dental practitioners

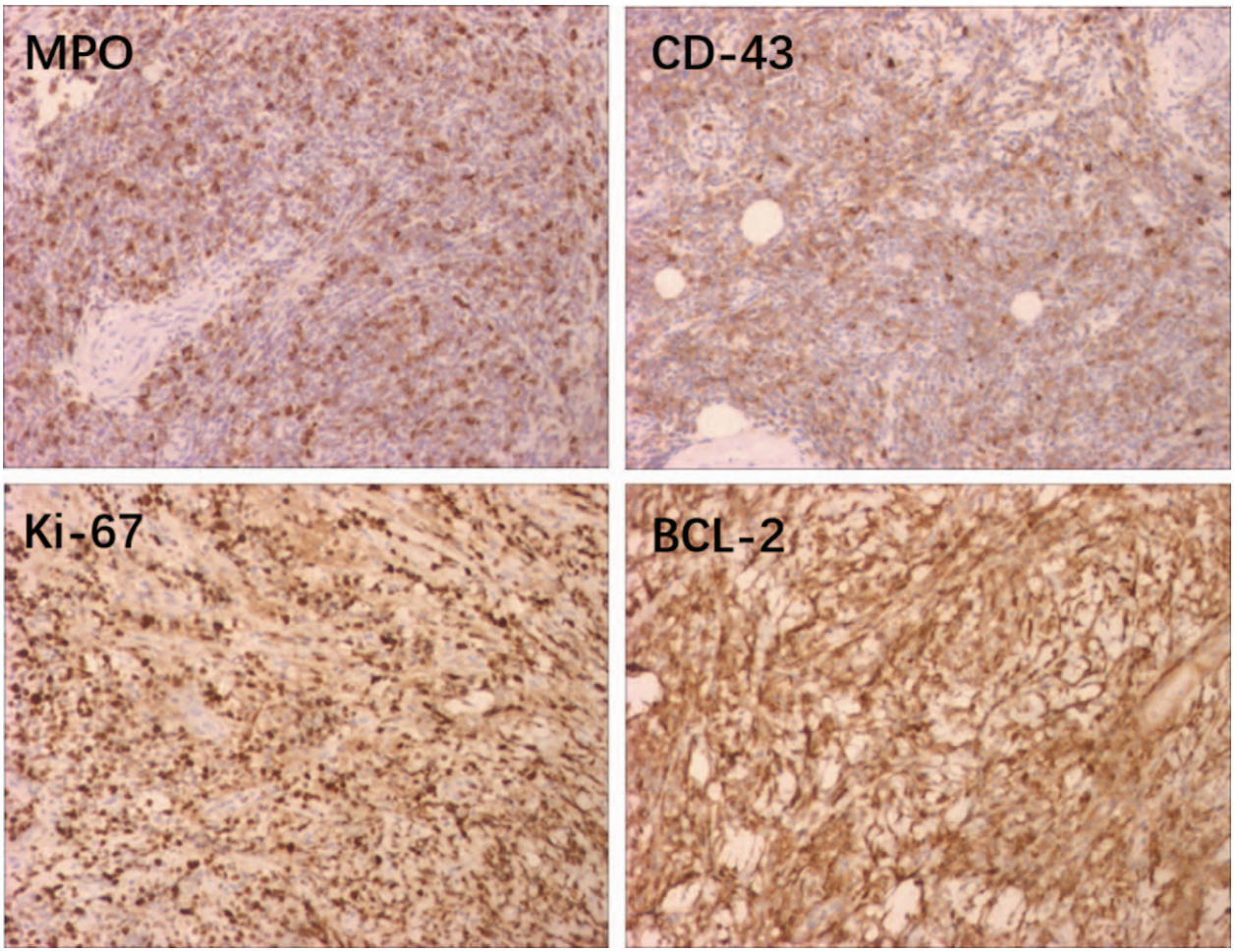

Figure 3. Immunohistochemical staining showed positivity for myeloperoxidase (MPO), BCL-2, CD4, and Ki-67. (magnifification: ×400).

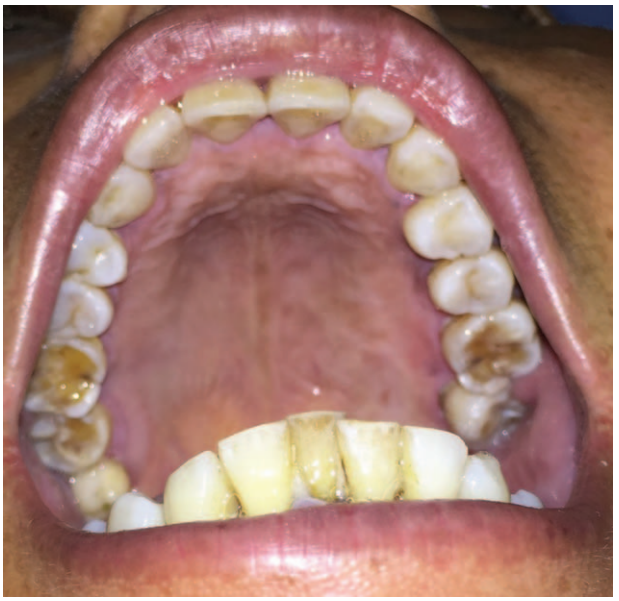

Figure 4. Interoral view after 2 cycles of chemotherapy.

is in differentiating malignant, infectious, and inflammatory lesions, which can often have overlapping clinical features.[44] To accurately diagnose oral primary GS, it is usually based on histopathological and immunohistochemical analysis, and a history of symptoms associated with hematological diseases that might be absent. Morphologically, oral primary GS exhibits variable numbers of primitive, poorly differentiated cells with granular cytoplasm, round to oval nuclei with well-defined membrane and prominent nucleoli, intermingled with reactive inflammatory infiltrate.[45] Different phases of myeloid differentiation are shown in tumor cells containing the eosinophilic myelocytes and blastic cells with minimal granulocytic differentiation. It seems difficult to differentiate the histopathological diagnosis of GS from that of large B-cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, and poorly differentiated squamous cell carcinoma. IHC can improve diagnostic accuracy.[16,25] IHC proves the granulocytic origin of tumor cells, which are usually positive for MPO, lysozyme, CD34, CD45, CD68, CD117, and some important markers for the diagnosis of oral primary GS (Table 1). Thereinto, MPO and lysozyme are specific markers of oral primary GS and are associated with the process of tumor cell differentiation.[3,6,45,46]

For nonleukemic GS, it is critical to comprehensively analyze both morphological and immunophenotypic results. In the present

Table 1

Clinical characteristics and diagnosis of reported cases with primary oral cavity GS.

Cases (first author, years)	Age(yr)/ Sex	Location	Size(cm)	Symptoms	Diagnosis basis
Brooks, 1974[11]	8/M	Maxilla R	—	Nostril, right upper molars tumor	HE
Conran, 1982[12]	2/F	Mandible R	2 × 3cm	Swelling of the right lower mandible	HE
Takagi, 1983[13]	25/F	Gingiva L	4 × 1cm	Swelling of the gingiva with pain	IHC - MPO
Reichart, 1984[14]	35/F	Mandible R	1.5 × 1.5cm	Brownish color tumor	CS - chloracetate esterase
Castella, 1984[15]	89/F	Hard palate L	2 × 1cm	Exophytic, ulcerated gray-white lesion	CS - chloracetate esterase
Rodriquez, 1990[16]	56/M	Gingiva L	5 × 3cm	Exophytic, reddish lesion with pain	IHC - lysozyme
Eisenberg, 1991[17]	33/M	Multiple gingiva	—	Multiple, raised, granular-appearing, red nodules	CS - Sudan black, MPO
Menasce, 1999[18]	63/F	Gingiva	—	NR	IHC - MPO
Tong, 2000[19]	76/F	Gingiva R	4 cm in diameter	Diffuse, ulcerative, granular-appearing lesion	IHC - MPO, CD45
Lee, 2001[20]	43/F	Gingiva L	3.5 × 1.5cm	Exophytic, firm, black-pigmented lesion	IHC - MPO, CD68, Mac387
Jordon, 2002[21]	62/F	Mandible apical	—	Periapical granuloma and chronic abscess	IHC - MPO, CD43, CD15
Antmen, 2003[22]	12/F	Gingiva	4 × 3cm	Bright red, soft, friable, edematous mass	IHC - MPO, lysozyme
Colella, 2005[23]	62/F	Gingiva	—	Large swelling in the upper vestibular region	IHC - MPO, lysozyme, CD45
Koudstaal, 2006[24]	36/M	Hard palate L	1 × 3cm	Blue-gray, mucosa intac, normal texture	IHC - CD45, CD43, HLA-DR
Goteri, 2006[25]	84/F	Hard palate R	—	Ulcerated, nodular, infiltrative mass	IHC - MPO, CD45, CD43, CD34
Yinjun, 2006[26]	44/F	Gingiva R	—	Progressive enlargement mass with pain, ulcer	IHC - MPO, CD68
Lu, 2009[27]	63/F	Gingiva R	—	Puce mass, surface graininess, easily bleeding	IHC - MPO, CD34, Bcl-2
Qiu, 2010[28]	16/F	Condyle L	—	Preauricular swelling, restriction mouth open	IHC - MPO
Colović, 2011[29]	55/F	Mandible L	—	Large mucosal tissue swelling	IHC - CD117, CD45, CD68, lysozyme
Guastafierro, 2013[30]	56/F	Gingiva	—	Large swelling in the upper vestibular region	IHC - MPO, CD45, CD68, lysozyme
Mei, 2013[31]	56/M	Maxilla L	4 cm in diameter	Soft and solid mass	IHC -CD34, CD45, CD56, CD117, MPO
Chaudhuri, 2013[32]	60/M	Lip	—	Non-tender, firm, lumpy swelling	CS - Immature myeloid cells
Sharma, 2014[33]	9/M	Maxilla L	3 × 3cm	Single ill-defined, diffuse swelling	IHC - CD31, MPO, vimentin, CD99
Ponnam, 2014[34]	45/F	Gingiva L	5 × 5cm	Lobulated, firm, nontender and erythematous growth	IHC - CD45, CD68, CD117, MPO
Moshref, 2014[35]	45/M	Gingiva, Palate	—	Red and soft with irregular surfaces	IHC - CD45, C-Kit
Wang, 2014[I[36]	27/M	Buccal mucosa L	3 cm in diameter	Firm mass without tenderness	IHC - MPO, CD34, CD68, CD117
Dineshkumar, 2016[37]	62/F	Gingiva	—	Gingival enlargement without purulent discharge	IHC - MPO, CD43
Sengupta, 2016[38]	2/M	Mandible L	4 × 2.5cm	Firm to hard, circumscribed, mildly tender swelling	IHC - CD45, CD68, lysozyme
Aboelhassan, 2017[39]	67/F	Hard palate R	4 × 5cm	Red painless swelling	IHC - MPO, CD43, CD117
Kumar, 2017[40]	28/M	Mandible L	—	Ill defined bony hard swelling	IHC - CD45, MPO
Shen, 2018[41]	41/F	Gingiva	—	Blue-gray discoloration gradually developed	IHC - MPO, CD68, CD117, KI-67
Present case	49/F	Hard palate R	3 × 2cm	Ulcerated surface mucosa	IHC - MPO, CD4, Bcl-2, CD117

CS = cytochemical staining, F = female, HE = histologic examination, IHC = immunohistochemistry, L = left, M = male, NR = not record, R = right.

case, the pathomorphological examination was nonspecific, but IHC showed positive for EBER, MPO, CD4, BCL-2, CD117, which hinted that tumor cells were from the myeloid cells. IHC was negative for CD3 and CD20. This did not support the source of T and B cells.[47,48] Therefore, the definitive diagnosis was GS. Moreover, before the diagnosis of primary GS, we viewed the bone marrow image, chromosome karyotype analysis, and fusion gene detection. Bone marrow changes occurred before peripheral blood changes, and chromosome karyotype analysis and fusion gene detection could prompt diagnosis when there was no obvious abnormality in bone marrow cell morphology.[49]

With regards to available therapeutic options, there is an absence of a treatment guideline for primary GS with the recommended treatment regimen being conventional AML type chemotherapeutic protocols. As Table 2 shows, majority of patients have shown complete remission of the disease after the advent of Ara-c and anthracycline-based therapeutic regimens. It is recommended that early aggressive systemic chemotherapy contributes in the control of the progression of the disease and lengthens survival.[50,51] In some cases, radiotherapy alone can also produce good curative effect, but it cannot delay the transformation of primary GS into leukemia or improve the prognosis.[11,32] Clinically, radiotherapy combined with chemotherapy is an effective choice for clinical symptom relief and consolidation therapy. Surgical resection alone is insufficient.[31,36,39] Whether surgery depends on the size change of the tumor after radiotherapy and chemotherapy is unclear.

Although systemic chemotherapy can reduce the risk of GS conversion to AML, it cannot completely stop the progression of AML (averagely 10.5 months).[52] At the same time, chemotherapy has side effects such as cardiotoxicity and myelosuppression. Some patients die of sepsis before the end of chemotherapy.[11,22,29] Therefore, choosing a safe and effective treatment method that will prolong long-term survival is difficult. In recent years, with the development of bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT) technology, the treatment of primary GS has entered the era of comprehensive treatments such as combined radiotherapy and chemotherapy with BMT/HSCT. While there are no prospective trials evaluating the role of BMT/HSCT in primary GS, some retrospective studies have shown good results with a 5-year survival rate of 48% and even encourage considering allogenic BMT/HSCT after the patients' first induction of remission.[53–55]

Targeted therapy is a new orientation of primary GS treatment. These agents include histone deacetylase inhibitors, DNA methyltransferase inhibitors, FLT3 inhibitors, and farnesyltransferase inhibitors. However, it was most reported by cases lacking multicenter controlled trials.[50,56] With the deepening of the study of primary GS molecular mechanisms, targeted therapy may be a new effective therapy.

Table 2

Treatment management and prognosis of reported cases with primary oral cavity GS.

Cases (first author, years)	Age(yr)/Sex	Treatment	Remission/mo	Progression/mo	Retreatment	Outcome/mo
Brooks, 1974[11]	8/M	RT	—	—	—	A&W/48
Conran, 1982[12]	2/F	CT + RT	CR/2	—	—	A&W/16
Takagi, 1983[13]	25/F	CT	—	AML/18	CT+RT	DOD/24
Reichart, 1984[14]	35/F	Surgery + CT	CR/4	AML/8	CT	DOD/13
Castella, 1984[15]	89/F	NR	—	—	—	DOD/2
Rodriquez, 1990[16]	56/M	CT	—	—	—	Die of sepsis/17 d
Eisenberg, 1991[17]	33/M	CT	CR/4	—	BMT	A&W/20
Menasce, 1999[18]	63/F	NR	—	AML/24	NR	A&W/15 yrs
Tong, 2000[19]	76/F	CT + RT	R/2	AML/7	NR	DOD/17
Lee, 2001[20]	43/F	CT+RT	CR/6	—	—	A&W/6
Jordon, 2002[21]	62/F	NT	—	MML/2	CT	DOD/10
Antmen, 2003[22]	12/F	CT	R/2	Progession	CT	Die of sepsis/4
Colella, 2005[23]	62/F	CT	—	—	—	DOD/7
Koudstaal, 2006[24]	36/M	CT + RT	CR/24	Bone marrow relapse	CT	NR
Goteri, 2006[25]	84/F	Surgery + RT	CR/-	—	—	A&W/7
Yinjun, 2006[26]	44/F	CT	CR/-	—	—	NR
Lu, 2009[27]	63/F	CT	CR/2	—	—	A&W/6
Qiu, 2010[28]	16/F	Surgery + CT	CR/2	—	—	NR
Colović, 2011[29]	55/F	CT	—	—	—	Die of sepsis/8
Guastafierro, 2013[30]	56/F	CT	—	—	—	DOD
Mei, 2013[31]	56/M	Surgery + CT	CR/4	—	—	NR
Chaudhuri, 2013[32]	60/M	RT	CR/8	—	—	NR
Sharma, 2014[33]	9/M	CT + RT	CR/5	—	—	A&W/24
Ponnam, 2014[34]	45/F	CT	—	—	—	DOD/2
Moshref, 2014[35]	45/M	CT	—	—	—	Die of heart attack/2
Wang, 2014[[36]	27/M	CT + RT	CR/2	—	—	A&W/15
Dineshkumar, 2016[37]	62/F	NR	—	—	—	NR
Sengupta, 2016[38]	2/M	CT	CR/2	—	—	A&W/-
Aboelhassan, 2017[39]	67/F	Surgery+ RT + CT	—	Multiple occurrence	CT	NR
Shen, 2018[41]	41/F	CT	R/4	—	—	A&W/12
Present case	49/F	CT	CR/2	—	—	A&W/12

A&W = alive and well, AML = acute myeloid leukemia, CR = complete remission, CT = chemotherapy, DOD = die of disease, F = female, M = male, MML = myelomonocytic leukemia, NR = not record, R = remission, RT = radiotherapy.

4. Conclusion

Oral primary GS is a rare tumor with poor clinical outcome. It has protean clinical manifestations and histological overlap with numerous tumors making it a diagnostic challenge for clinicians and pathologists alike. Careful morphological and immunohistochemical analyses, correlating with clinical data are necessary to establish the diagnosis of oral primary GS. Early aggressive systemic chemotherapy can effectively relieve symptoms, significantly reducing primary GS conversion into AML and prolonging overall survival. However, there is no uniform standard on radiotherapy whether combined with systemic chemotherapy synchronously or after the therapy. There is no verdict that BMT/HSCT should be used as preferred alternative for the treatment of disease progression after chemoradiotherapy. Moreover, there is a lack of effective management over long-term treatment. Considering the abovementioned findings, there is a need for further studies to be done.

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Writing – review & editing: Xiao-lin Li.

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