CASE REPORT

Granulocytic sarcoma (chloroma) of the oral cavity: Report of a case and literature review

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Summary A case of granulocytic sarcoma (chloroma) of the palatal mucosa is reported. Granulocytic sarcomas are composed of a localized collection of immature myeloid cells and are considered to be specific lesions of AML or the onset of a blast crisis in chronic myelogenous leukemia (CML). Localization in the oral cavity is rare. A review of the literature showed only thirty-six cases of granulocytic sarcoma in the oral cavity. In this paper we present patient’s data and an overview of the literature.

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KEYWORDS
Granulocytic; Sarcoma; Chloroma; Oral cavity; Palatal swelling; Review

Clinical presentation

A 36-year-old male was referred to the Maxillofacial Surgery outpatient’s clinic by the ENT doctor because of a palatal and submandibular swelling.

The patient stated that the palatal swelling had been there since the extraction of a maxillary molar, nine months prior to his visit to our clinic. The lesion had increased in size and was painful. There had been no bleeding or purulent discharge from the lesion. The submandibular swelling was noted by the patient five months earlier and had also slowly increased in size. The patient had lost two kilograms in weight in five months. On examination there were several painless, firm and mobile lymph
nodes in the right submandibular region, with the largest dimension measuring from 1 to 3 cm. The intra-oral swelling was firm and immobile. It was located on the left hard palate and its largest dimension was 3 cm. The swelling had a blue-gray appearance, the overlying mucosa was intact and had a normal texture (Fig. 1). Further clinical examination yields no other pathological findings. The panoramic X-ray did not show any evidence of bone involvement. The medical history of the patient mentioned a Bell’s palsy two years prior to the onset of the present lesions. The patient was not on any medication.

**Differential diagnosis**

The clinical differential diagnosis in our case with the palatal swelling includes soft tissue tumors like lymphomas of the palate (non-Hodgkin’s lymphoma or malignant histiocytosis),\(^1\) benign minor salivatory gland tumors (e.g., pleomorphic adenoma), malignant minor salivatory gland tumors (e.g., mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell adenocarcinoma), palatal abscesses, myeloid leukemia (e.g., acute myeloid leukemia, or chronic myeloid leukemia) and acute lymphoblastic or monocytic leukemia. Rare entities like Kaposi’s sarcoma, squamous cell carcinoma,\(^2,3\) benign lympho-epithelial lesion of the palate and ‘tumor-like’ lesions such as haemangioma should also be considered.

Although tumors of the salivatory glands are uncommon, they are by no means rare. The most common site for salivatory gland tumors is the parotid gland, accounting for 64–80% of all cases. A relatively low percentage, 15–32%, of these tumors are malignant. 8–11% occur in the submandibular gland, but the frequency of malignancy is 37–45%. Tumors of the sublingual glands are rare, comprising only 1% of all salivary neoplasms but 70–90% are malignant. The palate is the most frequent site for minor salivatory gland tumors, 42–54% of all cases. They mostly occur on the posterior lateral hard or soft palate, which have the greatest concentration of glands. The most frequently found tumors of the minor salivatory glands are the mucoepidermoid carcinoma, adenoid cystic carcinoma and acinic cell adenocarcinoma.\(^4\)

Because the patient did not exert any fever an inflammatory origin (abscess) was ruled out. Since the tumor was not localized (the combination of the palatal lesion with the submandibular lymph nodes), benign tumors (e.g., pleomorphic adenoma, benign lympho-epithelial lesion and haemangioma) were unlikely. The blue-gray appearance of the palatal lesion made the diagnosis of pleomorphic adenoma even less likely. The firmness of the palatal lesion and the fact that needle aspiration did not provide blood or pus ruled out the diagnosis of an abscess or haemangioma. Malignant histiocytosis and squamous cell carcinoma were less likely since the palatal mucosa overlying the tumor was intact without signs of ulceration. Virological examination revealed the patient to be HIV negative making the diagnosis of Kaposi’s sarcoma less likely.

Fine needle aspiration from a submandibular lymph node did not provide enough tissue for diagnosis so a lymph node from the right submandibular region (level II) was removed and sent in for histological examination. An incisional biopsy was taken from the palatal lesion and was sent for histological examination after standard pathological processing. The tissue was fixed in 10% neutral buffered formalin and embedded in paraffin after overnight tissue processing. Sections of four micrometers were cut, mounted on glass slides and stained with hematoxylin/eosin (HE) for standard pathological examination. Additional immunohistochemical staining were performed according to standard two step procedures using commercially obtained antibodies against the various receptor molecules in the cell and on the cell surface.

**Diagnosis**

Histological examination of both the palatal and the submandibular specimen showed a dense
cellular infiltrate extending from just under the epithelial layer till deep into the soft tissues (Fig. 2). The cells have a moderately amount of cytoplasm and a round to oval shaped, slightly polymorphic nucleus with inconspicuous nucleoli (Fig. 3). The nuclear chromatin pattern was relatively fine.

Histological differential diagnosis includes histiocytic or lymphocytic lymphoma. The tumor cells did not have a characteristic phenotype and may mimic cells of a large number of other tumors, especially when morphologic variants are involved. Among the tumors to be considered are amelanotic melanoma, alveolar rhabdomyosarcoma or plasmacytoma, small-cell carcinoma, epidermoid carcinoma, sarcoma, cystosarcoma, phyllodes, eosinophilic granuloma, atypical carcinoid, microglioma, Ewing’s sarcoma, multiple myeloma, immunoblastic sarcoma, reticulum cell sarcoma.

To make a final diagnosis a panel of antibodies was used in immunohistochemical staining procedures. The tumor cells did not stain with antibodies against pan-keratin, keratin 7, keratin 20, NCL5D3, CEA or EMA, making the diagnosis of carcinoma very unlikely. A melanoma was excluded with a negative staining for S100, HMB 45 and Melan A. A negative CD79a, and CD138 practically excluded a B lymphoma, including a plasmacytoma. A T-cell non-Hodgkin’s lymphoma was very unlikely because the CD2, CD3, CD5 and CD8 were negative. A negative CD30 and ALK-1 practically excluded an anaplastic large cell lymphoma. The tumor was however positive for CD 45 and in combination with the morphological features of the tumor cells the possibility of granulocytic sarcoma was raised, notwithstanding the fact that the Leder’s stain was negative. This was confirmed by a positive staining for CD43, HLA-DR and CD4 (partially) (Fig. 4). The negative staining for CD34, CD 117, MPO, lysozyme, glycophorin C, Factor VIII, Ulex Europeus makes a monocytoid differentiation the most likely. This is also supported by the negative Leders’s stain. This was confirmed by the flowcytometric analysis of the lymph node exhibiting CD45 and CD33 weakly, demonstrating positivity for CD117, CD56, CD13 and HLADR, while negative for CD34, cyMPO,
CD14, CD15 and CD16. The cytogenetic examination of the granulocytic sarcoma revealed complex karyotypic abnormalities, rendering the illness to a poor risk category.

The blood cell count revealed hemoglobin 9.3 mmol/l (8.6–10.5 mmol/l), platelets \(471 \times 10^9/l\) (150–370 \(\times 10^9/l\)), leukocytes \(7.8 \times 10^9/l\) [3.5–10.0 \(\times 10^9/l\)] with a normal differentiation. Virological examination revealed the patient to be HSV, HIV negative, HbsAg negative and anti HBc negative. Further laboratory examination revealed no hepatic nor renal disturbances and no signs of disseminated intravascular coagulation were established. A morphological smear of the iliac crest did not reveal an excess of blasts (4.2% of nucleated cells), the bone marrow biopsy showed a trilinear hematopoiesis without an increase in blasts. Cytogenetic and molecular diagnostic studies (AML1-ETO and CBFB-MYH11) from the bone marrow demonstrated no abnormalities. Immunological examination by flowcytometry, however, of the bone marrow revealed a undifferentiated myeloid population with the same immunological phenotype as was previously established on the lesion of the palate (markers used for minimal residual disease were CD34 negative, CD117 positive, weak expression of CD45 and positivity for CD56).

This demonstrates a small amount of leukemic blasts in the bone marrow, which do not reach the criteria of an acute myeloid leukemia, because the percentage of blasts did not exceed 20%. In addition, a morphological examination of the cerebrospinal fluid demonstrated the presence of blastic cells. CT-scan showed multiple enlarged cervical lymph nodes at levels one through five of the neck on the right side with the largest about 3 cm in diameter. There was a hepatomegaly of 20 cm on the CT-scan.

This led us to conclude that the final diagnosis was granulocytic sarcoma in the left hard palate and right submandibular region, with a small number of leukemic blasts in the bone marrow and the central nervous fluid.

### Clinical course and management

The patient was referred to the department of Hematology. The patient received two session of chemotherapy (first course: idarubicine \(1 \times 12 \text{ mg/m}^2\) on day 1–3, arabinosyl—cytosin \(200 \text{ mg/m}^2\) continuous on day 1–7; second course: arabinosyl—cytosin \(2 \times 1000 \text{ mg/m}^2\) day 1–6 and amsacrine \(1 \times 120 \text{ mg/m}^2\) day 1, 3 and 5). Intrathecal methotrexate 15 mg and dexamethason 4 mg was administered ten times because of the positive liquor, which became negative on this treatment. Because of the poor risk features of the granulocytic sarcoma a search for an allogeneic donor was undertaken, but no HLA-identical siblings or ‘‘matched unrelated’’ donors (MUD-donor) could be identified. Since there was no donor available for an allogeneic stem cell transplantation the patient received a third course of chemotherapy. The therapy was complicated by ARA-C toxicity, Aspergillus pneumonia, and a paronychia of the right hallux. Because of the central nervous system localization the patient received adjuvant radiotherapy (2 Gy, 15 fractions) of the brain and neck after the three courses of chemotherapy. There were no radiotherapy-related complications.

The disease went into complete remission for two years. But recently a bone marrow relapse was diagnosed, for which the patient is currently reinduced with high dose chemotherapy in order to perform an autologous or, if a MUD-donor can be located, an allogeneic stem cell transplantation.

### Discussion

Granulocytic sarcoma (chloroma) is an extramedullary-localized tumor mass composed of immature cells of the granulocytic lineage (myelocytes). Burns reported the first case in 1811.8 In 1853, King used the term chloroma because the tumor exhibited a greenish color that faded on exposure to the air, which was produced by the presence of myeloperoxidase (verdoperoxidase) in the tumor cells.9 The present term granulocytic sarcoma is more appropriate since the tumor is not always green, is composed of immature cells of the granulocytic lineage, and resembles a sarcoma.6 Granulocytic sarcomas are thought to arise in the bone marrow and travel via the Haversian canals to reach the subperiosteal region of bone. Once in the periosteum, the tumor cells can spread to other parts of the body.1,12 The association of granulocytic sarcoma with leukemia was first made in 1892 by Dock.1,13 It has most frequently (2.9–8%) been reported with the monocytic form of acute myelogenous leukemia (AML M5) but also association with chronic myelogenous leukemia (3.9%) and at the onset of a blast crisis in chronic myelogenous leukemia is reported (4.2%).6,10,14 Several
cases are reported without detectable evidence of leukemia in the peripheral blood or bone marrow.\textsuperscript{6,15} The granulocytic sarcoma may precede the manifestations of AML by months or years.

The pathological diagnosis of granulocytic sarcoma should be made on both histological and (immuno)histochemical grounds. In the HE staining of optimally fixed, processed, embedded and cut tissue, one should observe at least blasts, with a high nuclear/cytoplasmic ratio and more or less round nuclei with a diameter of approximately twice the diameter of a normal lymphocyte. The chromatin should be relatively fine. Course chromatin pattern usually indicates a blast of lymphocytic origin. To refine and confirm the morphological differential diagnosis, immunohistochemistry is imperative when, as in this case, the histochemical Leder’s (chloro-acetate esterase) stain does not demonstrate the granules in the cytoplasm. The Leder’s stain is often if not always negative if the lesion demonstrates (complete) differentiation which is not myelogenic or when the lesion consists of very immature blasts. Alternatively, flowcytometry may also be used when fresh tissue is available.

When relying on immunohistochemistry to confirm the histological diagnosis, one may start with confirmation of haematological origin by demonstrating a positive staining for CD45. Additionally, one or more of the markers indicative of a myeloid origin are usually positive: myeloperoxidase (MPO), lysozyme, CD13, CD14, CD33, CD34, CD68 and CD117.

It is remarked that CD13, CD14 and CD33 are only available for use on frozen sections, while CD117 is also positive for a GIST (gastrointestinal stromal cell tumor). Therefore, in practice a positive staining of a combination of these markers together with the compatible morphology is used to make the diagnosis: CD34, CD43, CD4, MPO, lysozyme, glycophorin C.

A positive CD43 staining is important in making the diagnosis of granulocytic sarcoma in a number of cases, especially when other myeloid markers such as MPO does not stain However, this is only the case in the context of a negative staining pattern for a panel of markers, which are specific and sensitive enough for of B and T cells. The same goes for CD4.\textsuperscript{16}

We use glycophorin C as glycophorin A does not stain all the erythroid precursors and thus does not give a complete picture of the erythropoieses in a bone marrow biopsy.\textsuperscript{17} More importantly, malignancies derived from erythroid precursor may have a higher chance to be false negatively stained with glycophorin A.

In practice, it may be necessary to also exclude other tumors in the morphological differential diagnosis with negatively staining antibodies. This include carcinoma’s (negative keratins), amelanotic melanoma (negative S100 and MelanA), anaplastic large cell lymphoma, small cell variant (negative CD30 and ALK-1), B-cell lymphoma’s (negative CD20, CD79a and CD138), and T cell lymphoma’s (negative CD1a, CD2, CD3, CD5, CD8 and if necessary granzyme B and TIA-1).\textsuperscript{18}

Oral manifestations of acute leukemia are well documented in literature.\textsuperscript{19,20} The myeloid leukemias are usually of medullary origin with primary dissemination of immature blast cells in various tissues of the body.\textsuperscript{21} Extramedullary tumors occurring before or during myeloid leukemia were termed granulocytic sarcomas, leukocytic sarcomas, chloromas or myelosarcomas.

In literature there are several reported cases of facial nerve paralysis as the presenting symptom of leukemia.\textsuperscript{22–26} In these cases the actual location of the tumor caused the facial nerve palsy through compression. The medical history of our patient mentioned a Bell’s palsy two years prior to the onset of malignancy. The location of the granulocytic sarcoma (neck and palate) and the elapsed period of time between the nerve palsy and the onset of the malignancy can, in our opinion, does not explain the facial nerve palsy. Therefore we conclude that the Bell’s palsy in our case was coincidence.

A structural search of the literature (Medline) was performed and showed only thirty-six cases of granulocytic sarcoma in the oral cavity reported from 1883 until now, of which five were situated on the hard palate. The patient date of the previously reported cases and the case presented here are listed in Table 1. The clinical features of the granulocytic sarcoma the oral cavity reported are diverse. The most frequently reported clinical presentation of the tumor is of a firm swelling with either a bluish, brownish, reddish, black-pigmented or gray-white color with intact overlying mucosa. Several authors describe nodular exophytic growing lesions with or without ulceration and bleeding. Others report non-healing extraction sockets with a polypoid mass growing from it. Also a purulent apical lesion has been described to be the clinical presentation of the granulocytic sarcoma. Of the five reported palatal lesions three presented themselves as a firm gingival swelling with intact overlying mucosa,\textsuperscript{29,39,48} one with a bulging bosselated surface,\textsuperscript{37} and one with an exophytic, ulcerated gray-white lesion.\textsuperscript{15}
Granulocytic sarcoma (chloroma) of the oral cavity is a rarely occurring entity. The oral diagnostician is confronted with a diagnostic challenge, when it presents itself as a solitary lesion, often well in advance of other the clinical and laboratory findings indicating a leukemia. This challenge is equal for both the physician and the pathologist. The tumor is often misdiagnosed as lymphoma or no diagnosis is reached before the onset of other clinical manifestations. The myeloid origin of these cells can be established with a histochemical Leder's staining, flowcytometry or immunohistochemistry.

Table 1  Reported cases of granulocytic sarcoma (GS) in the oral cavity

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Type of malignancy</th>
<th>Time of diagnosis of leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiari et al.</td>
<td>6</td>
<td>M</td>
<td>Left maxillary AB</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brooks et al.</td>
<td>8</td>
<td>M</td>
<td>Right maxillary sinus</td>
<td>AML</td>
<td>4 years after GS</td>
</tr>
<tr>
<td>Neiman et al.</td>
<td>83</td>
<td>F</td>
<td>Right maxillary AB</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hansen et al.</td>
<td>2</td>
<td>F</td>
<td>Right mandible</td>
<td>DF</td>
<td>16 months after GS</td>
</tr>
<tr>
<td>Conran et al.</td>
<td>25</td>
<td>F</td>
<td>Left mandible</td>
<td>AML</td>
<td>18 months after GS</td>
</tr>
<tr>
<td>Takagi et al.</td>
<td>35</td>
<td>F</td>
<td>Right mandible</td>
<td>AML</td>
<td>3 months after GS</td>
</tr>
<tr>
<td>Castella et al.</td>
<td>89</td>
<td>F</td>
<td>Left hard palate</td>
<td>DF</td>
<td>NR</td>
</tr>
<tr>
<td>Welch et al.</td>
<td>3</td>
<td>F</td>
<td>Left maxillary sinus</td>
<td>DF</td>
<td>NR</td>
</tr>
<tr>
<td>Timmis et al.</td>
<td>52</td>
<td>M</td>
<td>Left mandible</td>
<td>LL</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Muller et al.</td>
<td>37</td>
<td>F</td>
<td>Tonsil</td>
<td>AML</td>
<td>6 years before GS</td>
</tr>
<tr>
<td>Ficarra et al.</td>
<td>67</td>
<td>F</td>
<td>Right hard palate</td>
<td>AML</td>
<td>15 months after GS</td>
</tr>
<tr>
<td>Saleh et al.</td>
<td>62</td>
<td>F</td>
<td>Right mandible</td>
<td>AML</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Dreizen et al.</td>
<td>69</td>
<td>M</td>
<td>Right epiglottis</td>
<td>CML</td>
<td>3 years before GS</td>
</tr>
<tr>
<td>Ferguson et al.</td>
<td>4</td>
<td>F</td>
<td>Left maxillary AB and palate</td>
<td>AML</td>
<td>1 year before GS</td>
</tr>
<tr>
<td>Alessi et al.</td>
<td>4</td>
<td>F</td>
<td>Right maxillary AB and sinus</td>
<td>AML</td>
<td>2 years before GS</td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>56</td>
<td>M</td>
<td>Left mandible</td>
<td>AML</td>
<td>5 months after GS</td>
</tr>
<tr>
<td>Cho et al.</td>
<td>3</td>
<td>M</td>
<td>Right mandible</td>
<td>AML</td>
<td>2 years before GS</td>
</tr>
<tr>
<td>Eisenberg et al.</td>
<td>33</td>
<td>M</td>
<td>Right maxillary/mandibular AB</td>
<td>AML</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Stack and Ridley</td>
<td>70</td>
<td>M</td>
<td>Right mandible</td>
<td>CML</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Ritter et al.</td>
<td>41</td>
<td>F</td>
<td>Mandibular gingiva</td>
<td>AML</td>
<td>Before GS (time NR)</td>
</tr>
<tr>
<td>Tuset et al.</td>
<td>77</td>
<td>M</td>
<td>Right mandible</td>
<td>MDS</td>
<td>2 months before GS</td>
</tr>
<tr>
<td>Roth et al.</td>
<td>47</td>
<td>M</td>
<td>Gingiva (location NR)</td>
<td>AML</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Wiernik et al.</td>
<td>1</td>
<td>M</td>
<td>Mandible (location NR)</td>
<td>AML</td>
<td>22 months before GS</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>M</td>
<td>Gingiva (location NR)</td>
<td>AML</td>
<td>15 months before GS</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>M</td>
<td>Gingiva (location NR)</td>
<td>AML</td>
<td>15 months before GS</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F</td>
<td>Left mandibular gingiva</td>
<td>AML</td>
<td>21 months before GS</td>
</tr>
<tr>
<td>Lynch et al.</td>
<td>86</td>
<td>F</td>
<td>Left maxillary gingiva</td>
<td>AML</td>
<td>29 months after GS</td>
</tr>
<tr>
<td>Carmona et al.</td>
<td>60</td>
<td>F</td>
<td>Right mandible</td>
<td>CML</td>
<td>2 years before GS</td>
</tr>
<tr>
<td>Tong and Lam</td>
<td>76</td>
<td>F</td>
<td>Right maxillary AB</td>
<td>AML</td>
<td>7 months after GS</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>43</td>
<td>F</td>
<td>Left maxillary AB</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Amin et al.</td>
<td>58</td>
<td>M</td>
<td>Left hard palate</td>
<td>AML</td>
<td>Directly with GS</td>
</tr>
<tr>
<td>Jordan et al.</td>
<td>62</td>
<td>F</td>
<td>Apical teeth number 41</td>
<td>AML</td>
<td>6 weeks after GS</td>
</tr>
<tr>
<td>Asna et al.</td>
<td>72</td>
<td>F</td>
<td>Tongue</td>
<td>MDS</td>
<td>NR</td>
</tr>
<tr>
<td>Present case</td>
<td>36</td>
<td>M</td>
<td>Left hard palate</td>
<td>AML</td>
<td>Directly with GS</td>
</tr>
</tbody>
</table>

Abbreviations: AML: acute myelogenous leukemia; NR: not reported; AB: alveolar bone; DF: disease free; LL: lymphocytic lymphoma; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome.

References
