

## CASE REPORT

## CASO CLINICO

# Maxillo-ethmoidal chloroma in acute myeloid leukaemia: Case report

## *Cloroma etmoido-mascellare in corso di leucemia mieloide acuta: caso clinico*

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## Key words

Paranasal sinuses • Malignant tumours • Chloroma • Myeloid leukaemia

## Parole chiave

*Seni paranasali • Tumori maligni • Cloroma • Leucemia mieloide*

## Summary

Chloroma, also called Granulocytic Sarcoma or Myeloid Sarcoma, is a rare malignant extra-medullary neoplasm of myeloid precursor cells. It is usually associated with myelo-proliferative disorders but its appearance may precede the onset of leukaemia. Chloroma may be found in several extracranial sites. Involvement of the head and neck region is uncommon. Differential diagnosis is often difficult and includes acute lymphoblastic leukaemia, large cell NHL, lymphoblastic lymphoma and Ewing's sarcoma. The case is presented of a maxillo-ethmoidal chloroma occurring in a case of poor prognosis acute myeloid leukaemia, emphasizing the clinical and cyto-histological features and problems concerning differential diagnosis.

## Riassunto

*Il Cloroma, anche detto Sarcoma mieloide o Sarcoma granulocitico, è un raro tumore maligno extramidollare costituito da cellule immature della serie granulocitaria. È usualmente associato ad un disordine mieloproliferativo ma può anche precedere l'inizio di una leucemia. Le localizzazioni extracraniche del cloroma sono molteplici, ma l'interessamento dei distretti cervico-facciali è poco comune. La diagnosi differenziale citoistologica può talvolta essere complessa, potendosi confondere con la leucemia linfoblastica acuta, con il sarcoma di Ewing e con diversi quadri di linfoma linfoblastico e a grandi cellule. Gli Autori descrivono un caso di cloroma etmoido-mascellare in corso di leucemia mieloide acuta, ad esito infausto, sottolineando gli aspetti citoistologici e clinici ed enfatizzando le problematiche di diagnosi differenziale.*

## Introduction

Chloroma is a rare malignant extra-medullary neoplasm of myeloid precursor cells. It was described for the first time by Burns in 1811<sup>1</sup> and, later, called Chloroma by King in 1853<sup>2</sup> on account of its green colour which is believed to be caused by myelo-peroxidase, an enzyme present in the myeloid cells. In 1966, it was included in the Rapaport classification and almost three decades later was called Granulocytic Sarcoma or Myeloid Sarcoma according to the WHO classification<sup>3</sup>.

This disorder often occurs in concomitance with an acute myeloid leukaemia and other myelo-proliferative disorders such as *polycythemia vera* (PV) and myeloid metaplasia<sup>3,4</sup>. On the other hand, it rarely develops in patients with no symptoms of leukaemia, either in the peripheral blood or in bone marrow. In

most of these patients, following the occurrence of chloroma, an overt acute myeloid leukaemia develops within 1 and 49 months. In any event, the presence of a chloroma is certainly the sign of poor prognosis<sup>5-8</sup>.

A case of maxillo-ethmoidal chloroma is described which developed during the course of acute myeloid leukaemia (AML), focusing on the clinical and cyto-histological findings and emphasizing the difficulties concerning differential diagnosis.

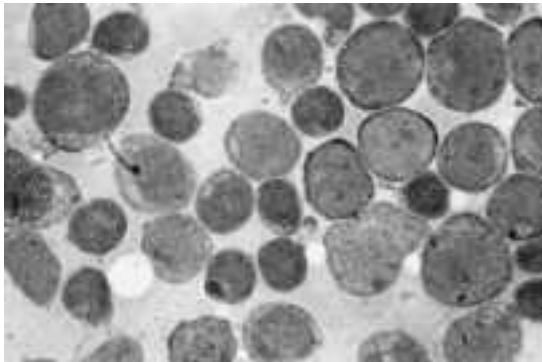
## Case Report

A 72-year-old female with M0 FAB AML under chemotherapy with hydroxycarbamide came to our attention at the Division of ENT, in August 2003, on account of right facial swelling and fever. The patient

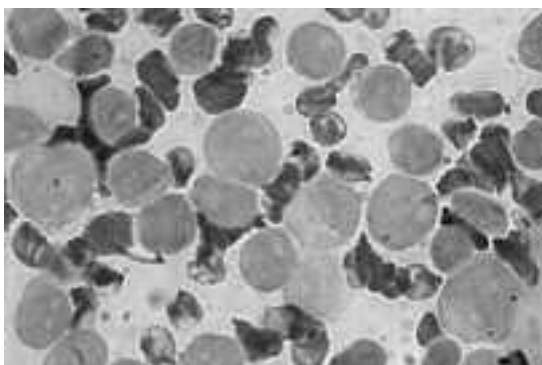
had been diagnosed, 12 months previously, with M0 FAB acute myeloblastic leukaemia and treated with only hydroxycarbamide.

The diagnosis of AML was made from results of bone marrow aspirate that showed abundant cells presenting a homogeneous infiltrate of small and middle blastic cells, with little basophil cytoplasm without granules, and a nucleus with loose chromatin and prominent nucleoli (Fig. 1) and immunophenotypic study either on peripheral blood or on marrow (that confirmed the diagnosis of M0 FAB acute myeloblastic leukaemia with evident immature myeloblasts positive for CD13, CD34, CD117, partially positive for CD33 and negative for CD7, with Perox-negative stain) (Fig. 2).

The physical examination showed hepatosplenomegaly. ENT examination showed a re-



**Fig. 1.** Acute myeloblastic leukaemia M0 FAB (McGrunwald-Giemsa x100): bone marrow aspirate shows homogeneous infiltrate of small and middle blastic cells, with little basophil cytoplasm without granules, and nucleus with loose chromatin and prominent nucleoli.



**Fig. 2.** Acute myeloblastic leukaemia M0 FAB with Perox-negative stain.

markable phlogistic swelling of the eyelid and of the right side of the face, with involvement of orbit, nasal cavity and maxillary sinus. The right nasal cavity was occupied by a solid, greyish, non-bleeding tissue. The posterior portion of the rhino-mesopharynx was covered by a purulent secretion. There were neither appreciable anomalies of the pharyngeal-laryngeal areas, nor cervical lymphadenopathy. The patient was admitted to our Department. Laboratory tests showed a remarkable leucocytosis (105.500) composed of immature myeloid elements (blasts) and by some polychromatophilic erythroblasts, a remarkable anaemia (haemoglobin 8.1 g/dl, erythrocytes 2,740,000, haematocrit 24.4%), hyperglycaemia (326) and hyperazotaemia (63). An urgent cerebral and maxillo-facial computed tomography (CT) scan revealed the presence of solid pathological tissue filling the right maxillary and ethmoidal sinuses, almost the entire homolateral nasal cavity including the front part of the orbit, between the medial wall and the eye; that tissue, the diameter of which did not exceed 2.5 cm, showed disappearing borders and displaced the eye and the medial right muscle laterally (Figs. 3, 4).

Ophthalmologic examination confirmed exophthalmus in the right eye with increased intra-ocular pressure (18 mm/Hg) associated with eyelid swelling and reduced eye motility.



**Fig. 3.** Coronal contrast-enhanced CT scan demonstrated non-specific isodense opacity in right nasal cavity, maxillary and ethmoidal sinuses. Orbit is displaced laterally by the lesion.



**Fig. 4.** Axial contrast-enhanced CT scan demonstrated non-specific isodense opacity in right nasal cavity and ethmoidal sinuses. Lesion infiltrates right medial muscle.

Intravenous antibiotic (cefotaxime 6 g, 3 times a day, amikacine 3 g, 3 times a day), antimycotic (fluconazole 400 mg/d) and steroid treatment (betamethasone 8 mg bid) was started; 5 units of packed red cells were infused. Hydroxycarbamide was increased to 2 g/d.

As an empyema of the maxillary sinus and anterior ethmoidal cells was likely to be present, a surgical transnasal and transmaxillary approach (according to Caldwell-Luc) was performed. Following a Caldwell-Luc surgical procedure and emptying of the right rhino-ethmoidal areas through the nasal way a large amount of greyish, non-bleeding necrotic-like parenchymatous tissue was removed. The pathologic examination was positive for a secondary extra-medullary location of AML or chloroma. Most of the tissue was necrotized; however, in the area in which the necrosis was less evident, an intra-vascular and interstitial infiltrate was present composed of round-shaped cells, not cohesive, with a reniform nucleus, mainly positive for CD34 and MPO. A different level of maturation between marrow blast and extranodal blast can be taken into account to explain the different peroxidase pattern.

No cytogenetic studies were carried out either on the bone marrow or on the neoplastic cells.

Despite medical and surgical treatment, the patient's clinical conditions gradually deteriorated, fever in-

creased, anuria occurred and the patient died 10 days after being hospitalised.

## Discussion

Chloromas are rare extra-medullary neoplasms with an incidence between 3 and 4.7% of the myelo-proliferative diseases<sup>9,10</sup>. In about 70% of cases, they occur during the course of AML or chronic myelo-proliferative disorders such as PV or agnogenic myeloid metaplasia, because of the capacity of immature myeloid cells to massively invade the extra-medullary organs. Several factors may contribute to the development of an extra-medullary disease, namely cytogenetic abnormalities and the cellular surface markers. In fact, chloromas develop mostly concomitantly with the FAB subtype M5a, M5b M4 and M2 of the AML<sup>9</sup>.

The incidence of chloromas is between 3-9.1% of all AML<sup>4,11,12</sup>, preferentially in young patients or in children with no difference between sexes<sup>13</sup>. The organs most frequently involved are bones and periosteum probably due to the anatomical proximity with the bone marrow. In fact, from the bone marrow, through the Haversian canals, the tumoural cells can infiltrate the periosteum, particularly of the skull, sternum, ribs, orbit, spine, sacrum and proximal portions of the long bones. From here, the chloroma cells spread to the blood invading any organs. The most common sites of tumour invasion are the peritoneum, pericardium, bronchus, bladder, mediastinum, kidneys and lung<sup>4,14-18</sup>.

The frequency of the head and neck region varies, according to the literature, between 12%<sup>7</sup> and 48%<sup>19</sup>. In this region, the most frequently affected sites are the soft palate, the rhinopharynx, orbit, salivary glands, scalp and face<sup>7</sup>. Uncommon sites of chloroma localization are: the jaw<sup>20,21</sup>, facial nervus<sup>22</sup>, lips<sup>23</sup>, nasal cavity<sup>24</sup>, maxilla<sup>25</sup> and temporal bone<sup>22</sup>.

The clinical manifestations of a chloroma are aspecific, consisting only in local pain and a local mass effect. In the case of rhinosinusal involvement, the epistaxis may be supported by several factors, particularly thrombocytopenia and ischaemic necrosis of the nasal mucosa secondary to leukaemic infiltrate. Furthermore, persistent infection of the upper respiratory ways may be observed which shows a poor response to standard medical treatment<sup>26</sup>. Macroscopic examination of a chloroma is characterized by a greenish mass due to the presence of the myeloperoxidase enzyme in the immature granulocytic cells. Very rarely, myeloperoxidase is absent and then the mass is not characterized by the classic green colour that gives it its name<sup>27</sup>.

As far as concerns cytologic findings, the chloroma is composed of dyshomogeneous cells with few cy-

toplasm elements, round to oval nuclei, a sharply delimited nuclear membrane, finely granular chromatin and prominent nucleoli<sup>28</sup>. When there is no concomitant leukaemia, diagnosis of chloroma may be difficult. Routine histological examination of these tumours shows a pleomorphic infiltrate of primitive cells of varying size and nuclear configuration<sup>29</sup>. Haematoxylin-eosin (H&E) staining does not identify granulocytic cells and the neoplasm may appear histologically as a sheet of round monomorphic cells with no recognizable pattern. The most frequent finding is a widespread infiltrate of mononucleate and granulocytic cells, variably mature, among which the typical eosinophilic myelocytes<sup>9</sup>.

The histological differential diagnosis may be difficult due to the poorly differentiated myeloblasts or in the absence of the greenish colour. The tumours that can be confused with chloroma are histiocytic lymphoma, poorly differentiated lymphoblastic lymphoma, lymphoma with large cells, Ewing sarcoma, some acute lymphocytic leukaemia as well as primitive neuroepithelial tumours<sup>5 30</sup>. However, fundamental for diagnosis, apart from the microscopic examination, is immunochemical staining. Use of staining with naphthol-ASD-chloro-acetate esterase (CAE) and with anti-lysozyme immunoperoxidase allows us to obtain a correct diagnosis of 75% and 85%, respectively. It is, in fact, known that mature and immature granulocytic cells, with the exception of myeloblasts, show a positive activity to the chloro-acetate esterase. This staining is useful to distinguish chloroma from histiocytic and non-histiocytic lymphoma<sup>31</sup>. All granulocytic cells, including myeloblasts and myelocytes, stain positive for lysozyme, whereas the lymphocytes are negative<sup>7</sup>. Furthermore, granulocytic cells are different from the monocyte due to the negligible reaction to the staining with the alpha-naphthol-acetate esterase<sup>32</sup>. In our case, a different level of maturation be-

tween marrow blast and extra-nodal blast can be taken into account to explain the different peroxidase pattern.

It is sometimes mandatory, on account of the very heterogeneous morphological characteristics of some chloroma, to use additional diagnostic techniques, such as ultrastructural studies by means of electron microscopy. More recently, analysis of the chromosomal translocations and the use of more refined immuno-histochemical staining have been adopted in the classification of these neoplasms in order to correlate the morphological characteristics to the clinical behaviour<sup>5 6 19 25</sup>.

CT and MR are not considered essential for diagnosis since they do not show specific signs for chloroma. In the CT scan, a massive tumour occupying the nasal cavities and the paranasal sinuses may be associated with the infiltrate of a particular bone with erosion of the structures of the maxilla<sup>25</sup>. In the intracranial chloroma, the CT scan shows isodense, or slightly hyperdense, lesions in relation to the surrounding cerebral parenchyma, with homogeneous "enhancement", generally without calcifications; in this case, differential diagnosis with meningioma, the lymphomas and metastatic tumours is necessary<sup>33 34</sup>. MR scan of an intracranial chloroma involving the orbit and/or the paranasal sinuses shows the presence of the hypointense lesions on T1-weighted images and the isointense lesions on T2-weighted images, in relation to the white matter<sup>13 35</sup>.

The prognosis of acute, non-lymphocytic leukaemia that is associated with chloroma, even if poor, has decisively improved thanks to the development of more adequate and effective associations of chemotherapeutic drugs<sup>25 36</sup>. Chloromas are radiosensitive and local radiotherapy can be associated with chemotherapy. The earlier detection of extra-medullary granulocytic sarcomas could better define the real prognosis of these rare neoplasms<sup>36</sup>.

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