

Orbital Granulocytic Sarcoma Presenting Simultaneously with Acute Megakaryoblastic Leukemia

Rogelio Paredes-Aguilera^{1*}, Norma López Santiago², Adriana Méndez-Meraz³, Eduardo López-Corella⁴, Armando De Uña-Flores⁵ and Lina Romero-Guzmán⁶

¹Head of Hematology Department, Instituto Nacional de Pediatría, Mexico City, Mexico

²Department of Hematology, Instituto Nacional de Pediatría, Mexico City, Mexico

³Blood Bank, Hospital Infantil Teletón de Oncología, Querétaro, México

⁴Department of Pathology, Instituto Nacional de Pediatría, Mexico City, Mexico

⁵Department of Radiology, Instituto Nacional de Pediatría, Mexico City, Mexico

⁶Chief Hematology-Oncology Laboratory, Instituto Nacional de Pediatría, Mexico City, Mexico

***Corresponding author:** Rogelio Paredes-Aguilera, Department of Hematology, Instituto Nacional de Pediatría, Av. Insurgentes Sur 3700, Insurgentes Cuicuilco, Coyoacán, 04530 Ciudad de México, CDMX, Mexico City, Mexico.

Tel: +52-55-1084-0900, ext: 1928 or 1329;

E-mail: sparedes@fedex.com;

ORCID ID: <https://orcid.org/0000-0002-1329-3629>

Article Type: Case Report

Compiled date: June 28, 2021

Volume: 2

Issue: 2

Journal Name: Clinical Case Reports Journal

Journal Short Name: Clin Case Rep J

Publisher: Infact Publications LLC

Article ID: INF1000094

Copyright: © 2021 Rogelio Paredes-Aguilera. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-4.0).

Keywords: Orbital granulocytic sarcoma; Acute megakaryoblastic leukemia; Severe myelofibrosis

Cite this article: Paredes-Aguilera R, Santiago NL, Méndez-Meraz A, López-Corella E, De Uña-Flores A, Lina Romero-Guzmán L. Orbital granulocytic sarcoma presenting simultaneously with acute megakaryoblastic leukemia. Clin Case Rep J. 2021;2(2):1–7.

Abstract

Orbital granulocytic sarcoma involving the central nervous system and coinciding with acute megakaryoblastic leukemia is a rare complication of this disease. We report a case of a previously healthy male infant 20-month-old who developed acute megakaryoblastic leukemia and in whom the initial diagnosis was difficult because of associated severe myelofibrosis. We focus on this report on the clinical and cyto-histological features and problems concerning differential diagnosis and the importance of risk group stratification to identify specific relapse risks and select the most appropriate treatment, intensive-timing chemotherapy regimen, or HSCT obtain good outcomes.

Introduction

Granulocytic Sarcoma (GS), previously known as chloroma, is a solid tumor of myeloid precursor cells described for the first time by Burns in the early 19th century and originally termed chloroma by Knight in 1853 due to its green color attributed to the enzyme Myeloperoxidase (MPO). Later changed to GS by Rappaport in 1966, following reports of cases in which the tumor was not green and had sarcoma's gross features [1–3]. This led to frequent misdiagnosis as high as 75% in a historical study in 1986 and lower incidence (25%–47%) in more recent reports. However, the diagnosis of GS in the absence of myeloid leukemia still poses a diagnostic challenge, and most patients were mistaken as suffering from malignant lymphoma [4–11]. Since Dock first noted the association of GS with Acute Myeloid Leukemia (AML) the tumor has been reported more frequently in patients with AML, especially in children and is described as a solid tumor of immature granulocytic precursor cells, not always composed of granulocytes so terms as extramedullary tumors or extramedullary leukemia have also been proposed [12–17]. It presents as an extramedullary mass, and a manifestation of any myeloproliferative disorder that most frequently affects the bones of the skull, sternum or ribs, peritoneum, lymph nodes, and occasionally soft tissues around the dura, sinuses and orbit, and is included as one of the major subgroups of myeloid neoplasms and acute leukemia in the WHO classification [3,11,14,18] GS is more common in pediatric patients, especially younger than 15 years old, and many cases have been reported in the head and neck region, but the most frequent presentation is unilateral exophthalmos due to orbit involvement (OGS) and occurs associated with Acute Myeloid Leukemia (AML), mainly AMLM2 or AML with a monocytic component (M4 or M5) [10,17,19–27].

Case Presentation

A previously healthy 20-month-old male presented with a 3-day history of fever and upper tract infection, for which antibiotic treatment was given, and fever and malaise subsided. In the following weeks, the patient developed progressive pallor and respiratory symptoms. He was seen two months later by his treating physician; physical examination revealed tachypnea, a grade III/IV systolic ejection heart murmur, and hepatomegaly 2 cm below the right costal margin. Complete blood count (CBC) reported hemoglobin (Hb) 5.2 gm/dL, hematocrit 17%, white blood cell count (WBC) $7.3 \times 10^9/L$ and differential leukocyte count showed $1.3 \times 10^9/L$ absolute neutrophils, 77% lymphocytes, 4.2% monocytes and $76 \times 10^9/L$ platelets. He was transfused with packed red blood cells 20 ml x kg on two occasions to correct anemia and respiratory symptoms and was referred to our hospital for further evaluation and admitted to the outpatient hematology department four weeks later, where a diagnostic work-up was established. At that time, the patient was asymptomatic and physical examination unremarkable; a CBC reported Hb 16.6 gm/dL, hematocrit 45.7%, WBC $6.5 \times 10^9/L$, and differential leukocyte count showed $2.1 \times 10^9/L$ absolute neutrophils, 55% lymphocytes, 10% monocytes, and $46 \times 10^9/L$ platelets. Blood chemistry, coagulation, iron and virus profiles (CMV, HV, EBV, Parvovirus), urinalysis and culture, folic acid, and vitamin B12 were normal or negative. A Bone Marrow Aspiration (BMA) showed scarce cellularity, absent megakaryocytes, lymphocyte predominance, myeloid maturation arrest with moderate granular asynchronism, and negative for hematologic malignancy. A repeated BMA yielded a dry tap, and a bone marrow biopsy yielded scarce material; extended screening tests looking for an underlying immune disease process was carried on, and he continued follow-up in the ambulatory hematology clinic. One month later, he was admitted to the emergency ward after a malar traumatism and facial swelling; ophthalmic examination revealed bilateral upper and lower eyelid oedema, probably secondary to

bone traumatism. Ocular movements were normal; no signs of periorbital cellulitis and oedema disappeared after 24 hours of hospitalization (Figure 1). Plain RX of facial bones was normal. Physical examination revealed hepatomegaly 2-3-2 cm and



Figure 1: After right malar traumatism.

splenomegaly 2 cm below the costal margin, and the test was negative. A CBC showed Hb 9.8 gm d/L, hematocrit 29% WBC $11.2 \times 10^9/L$, $5.4 \times 10^9/L$ absolute neutrophils, and differential leukocyte count 36% lymphocytes, 14% monocytes, and $14 \times 10^9/L$ platelets, and isolated blasts with cytoplasmic protrusion or blebs and 1.4% reticulocytes. CBC showed progressive anemia (Hb 9.8 gm/dL), thrombocytopenia ($14 \times 10^9/L$), a small number of circulating blasts, and splenomegaly. BMA was performed, which yielded a dry tap, and bone marrow biopsy reported myelofibrosis (Figure 2, Figure 3); all other laboratory tests, including BUN

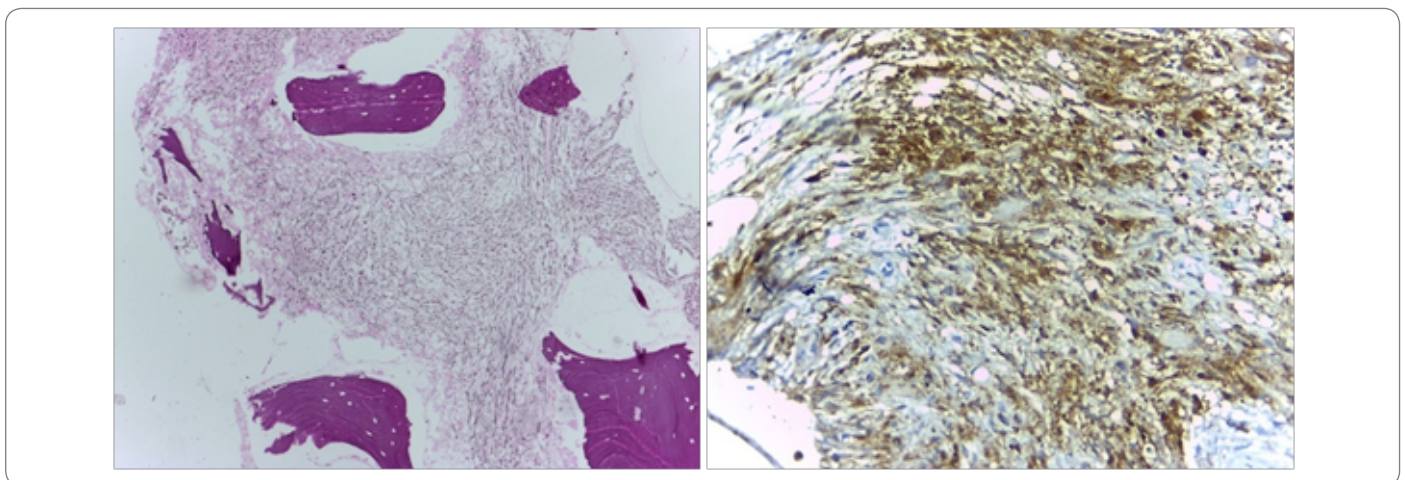


Figure 2 and 3: Bone marrow biopsy.

Histologic features: Decreased cellularity due to diffuse infiltration of the marrow by fibrous connective tissue replacing bone marrow elements. Special histochemical staining with tri-chrome Masson revealed collagen deposits with few scattered erythroid and myeloid precursors and dysplastic megakaryocytes.

and uric acid, were reported normal; he was transfused with packed red blood cells and discharged to continue follow-up in the outpatient hematology department. Two weeks later, he was seen in the outpatient department to present a rapidly progressive bilateral ocular proptosis, right eye pain, epiphora, chemosis, and severe bilateral upper and lower eyelid oedema (Figure 4), a left cervical enlarged lymph node, and pancytopenia. Blood smear analysis showed a steady increase in the number of circulating blasts during the following week (5%–10%–30%), some with cytoplasmic protrusion or blebs; BMA and the immunologic profile established the diagnosis of AMKL by the expression on blast cells of platelet specific markers CD41 (78%), CD42 (68%) and CD61 (98%) by multiparameter flow cytometry. Bone marrow biopsy was reported compatible with acute megakaryoblastic leukemia. Six hours after BMA and biopsy, the patient was admitted to the hematology ward because of continuous bleeding in the puncture site, which required treatment with platelet concentrates, and an urgent diagnostic work-up was programmed that included cranial simple and contrasted computed tomography (CT) scans and magnetic resonance imaging (MRI) of both orbits, excisional biopsy of the retroorbital tumor and left cervical excisional biopsy. Excisional OGS revealed GS with megakaryoblastic differentiation (Figure 5), and the left cervical excisional lymph node revealed a granulocytic sarcoma (Figure 6). MRI revealed a large irregular tumor with bilateral infiltration of upper jaw bones and orbits and extending to left posterior fossa (Figure 7, Figure 8).

The patient began an induction AML protocol with a 7 + 3 + 2 (cytosine arabinoside, daunorubicin, etoposide), an induction regimen, and triple intrathecal therapy (methotrexate, Ara-c,

hydrocortisone) twice a week for six doses and a 5 + 2 cytosine arabinoside and daunorubicin cycle. Hospitalization was complicated by anemia, bleeding, neutropenia, and systemic inflammatory response syndrome, which responded well to packed red cells, platelet concentrates transfusions and IV broad-spectrum antibiotics.



Figure 4: Bilateral OGS.

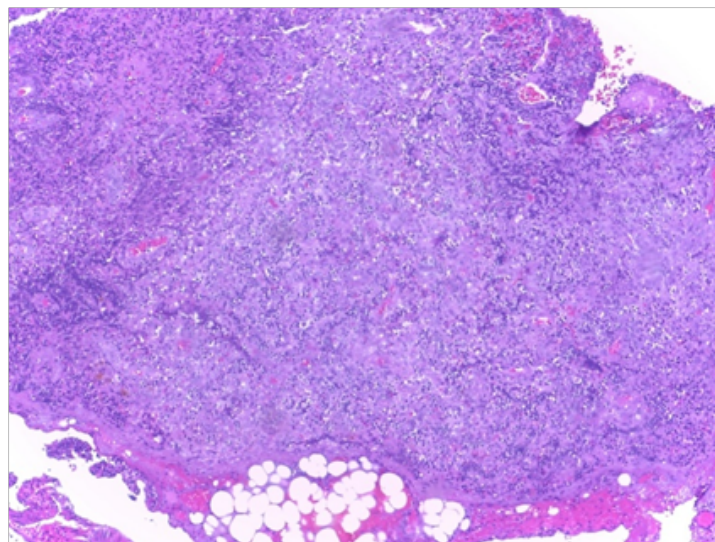


Figure 5: Excisional OGS biopsy.

Fragment of soft tissues with a neoplastic infiltration of medium to large blast cells with a variable nucleocytoplasmic ratio, an oval nucleus with fine stippled chromatin and 1 to 3 inconspicuous nucleoli forming a sheet cell lamina and numerous mitosis.

Microscopic description: GS with megakaryoblastic differentiation. Immunohistochemical staining was positive for CD45 (+++) and VIM (+++) diffuse, CD34 and CD31 positive focal and irregular, LMP-1 positive. Negative markers. CD3, CD20, CD30, CD15, CD1a, PS 100, CD21, CKSAE1/AE+, CD163, CD68, ALK, MPO, CD117, CD99. LMP-1 marker is frequently positive in bone marrow megakaryocytes of patients without a previous history of EBV infection and this expression is seen in undifferentiated megakaryocytes.

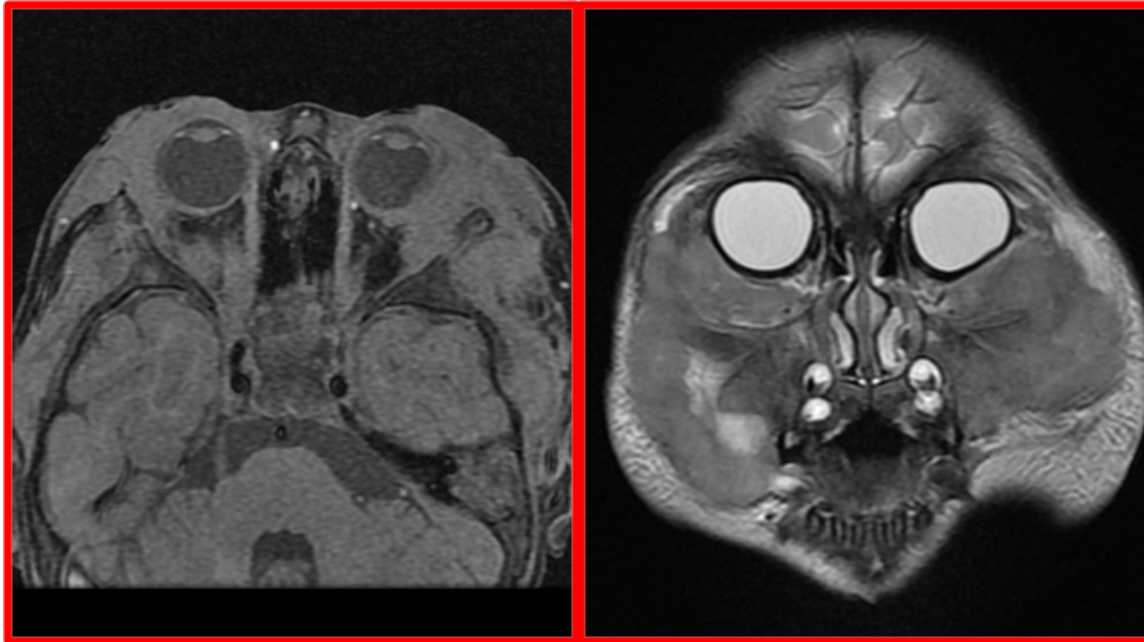


Figure 6 and 7: MRI of OGS.

Axial T1-weighted and Coronal T2-weighted SPIN ECO revealed an irregular homogeneous huge tumor infiltrating both orbits, bilateral malar, temporal areas and maxillary bones, of left predominance and extending into the posterior cranial fossa.

Two months after chemotherapy initiation, there was a significant clinical improvement with prompt resolution of both retroorbital and cerebral tumors, and the patient attained complete remission three months later (Figure 9). He continued consolidation therapy with high dose Ara-c (HDAC) + TIT and L-asparaginase rescue (Capizzi type II) for two cycles and etoposide+ Ara-c two cycles

with triple IT therapy. Maintenance therapy consisted of multiple combined chemotherapy with TAAP, COAP, POMP 5-day treatment and 9 days to 14 days rest and periodic triple IT therapy. After two years in Continuous Complete Remission (CCR), elective cessation of chemotherapy was programmed. He continues in CCR five years after stopping therapy.

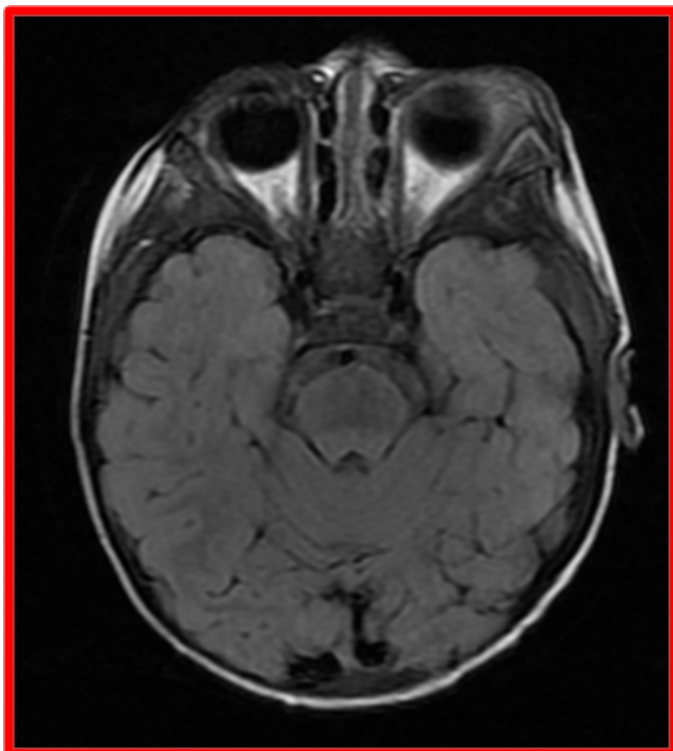


Figure 8: MRI T2-weighted Flair axial after 7 + 3 + 2 and 5 + 2 chemotherapy cycle two months after initiation of treatment with a remanent tumoral infiltration of the left orbit, pre and post septal.



Figure 9: Two months after initiation of induction treatment protocol.

Discussion

GS are rare solid tumors of immature myeloid precursor cells that presents as an extramedullary mass or a manifestation of myelodysplastic syndrome, chronic myeloid leukemia or any myeloproliferative disorder, and has been reported with an incidence of 2/1.000.000 in adults or 3%–9.1% in myeloproliferative disorders [4,11,28–30]. In the retrospective study of Dusenbery et al. of the Children's Cancer Group of 1832 patients with newly diagnosed AML, 199 (10.9%) had evidence of extramedullary leukemia, and these 12 (0.65%) corresponded to orbital GS. In contrast, Johnston et al. in a more recent study of the Children Oncology Group, reported that out of 1459 analyzed pediatric patients with AML, 99 (7.3%) presented myeloid sarcoma, 1% CNS sarcoma, and 2% OGS [17,31]. The mean age of presentation in childhood varies between 7 years and 8.8 years [23,32,33]. Orbit GS (OGS) has been reported to be more prevalent in countries from Asia, Africa, and Latin America, [32–36] and occurs associated with acute myeloid leukemia (AML), mainly AML-M2 with t (8;21) (q22;q22) or AML with a monocytic component (M4 or M5) [10,17,19–25,37].

GS can precede acute leukemia (*de novo*), present concurrently or during the disease (relapse) [3,5,9,10,12,23]. When GS occurs in patients with known AML or other myeloproliferative disorder, there is usually a little difficult for the clinician to establish and for the pathologist to make a correct diagnosis, but when GS precedes the development of AML or when it develops in a subtype of AML-AMKL-that frequently presents with severe myelofibrosis, diagnosis can be extremely difficult [3,5,8,9,11]. In our case, although the onset of symptoms, initial laboratory features, and a high clinical awareness suggested acute leukemia, it took four months to establish a definitive diagnosis. We attributed this to the slowly progressive clinical course of the disease extending over months, the presence of severe myelofibrosis, repeated BMA resulting in dry taps, and a late clinical event resembling "blast crisis" of chronic myeloproliferative disorders, as indicated by a steady increase in the number of blast cells in peripheral blood and BMA smears observed in the last month of follow-up, similar to the evolution of some cases of childhood AMKL as previously reported [38–40].

OGS is a rare event, and its presence in patients with a previous myeloproliferative disorder suggests an impending blast crisis or leukemic transformation, or the initial manifestation of relapse in a previously treated AML patient in remission, but in patients, without known hematologic diseases, it should alert clinicians to start a thorough, immediate search of AML, non-Hodgkin or histiocytic lymphoma, metastatic neuroblastoma, rhabdomyosarcoma, and small round blue cell tumors, by BMA and biopsy, tissue biopsy stained with H&E, and immunohistochemical methods, multiparameter flow cytometry, FISH, CT, and MRI scans, FDG-PET CT for an early diagnosis and prompt and optimal treatment.

One of the first cases of OGS and intracranial tumors in AMKL was

reported by Slavic et al. in 1991 in an 8-month child who responded well with a sharp reduction of intracranial masses two weeks after initiation of antileukemic therapy. However, unfortunately, the patient died of bacteremia 5 weeks after starting treatment. More recently, the case of Baldwin and Mian, that had a complete response to chemotherapy and local radiotherapy [24,41]. Although OGS is a rare event, in a series of 633 patients with AML treated in SJCRH over 30 years, 30 (4.7%) had one or more at some point in the course of their disease, and 13 (2%) had OGS, but despite its rarity, subcutaneous tissue and orbit were the most frequently affected sites. Another interesting issue of the report was that the tumor resolved completely within three months in 14/31(45.2%) patients treated with chemotherapy alone [42], as in the present case. Leukemic involvement of the central nervous system was common before effective chemotherapy protocols and was the first site of relapse in nearly 50% of children in remission previous to the incorporation of prophylactic therapy to the CNS in posterior protocols [43]. Masses within the brain are uncommon and were reported occasionally in acute leukemia until the middle of 1990s when two reviews and a casuistic of patients referred to its higher frequency in AML, its radiologic features, and highlighted the importance of early chemotherapy and radiotherapy to treat these complications [29,31,43–46].

It is difficult to speculate why our patient responded so well after the initiation of chemotherapy. May be because he was treated aggressively, or because his leukemia was not inherently aggressive, or because of both factors is not clear. Since the early 1990s, and based on different response rates observed in early-onset AMKL in infants with Down's syndrome and t (1;22) (p13; q13) or later in life, investigators were intrigued and started wondering if this was one or several diseases [47]. Although several subsequent reports indicated that the t (1;22) (p13;q13) was a nonrandom marker and restricted to infant AMKL, but that some cases expressed clinical and genetic heterogeneity, similar to some patients in our country [48–51]. In 2002 the Groupe Français de Cytogénétique Hématologique identified nine cytogenetic groups in childhood and adult megakaryoblastic leukemia, confirming different subtypes of the same disease, four of which were exclusively composed of children: (group 1) patients with Down's syndrome, (group 2) numerical abnormalities only, (group 3) t (1;22) (p13; q 13) (group 4) t (9;22) (q34; q11).

In the last decade, several groups of investigators have identified aggressive subtypes of pediatric AMKL, and four years ago, de Rooij et al. pointed out that recurrent abnormalities identified in nearly half of the patients by deep sequencing studies could be used for risk group stratification and included as a low/intermediate risk factor t (1;22) (p13; q13) resulting in a chimeric fusion RBM15/MKL1 and patients without any of the four specified cytogenetic abnormalities and patients with the CBFA2T3/GLIS2, rearranged KMT2A, NUP98/KDM5A, and monosomy 7 as high-risk factors in AMKL [52–55].

In conclusion, we can only speculate if the good response in our patient was the result of early intensive treatment as has been reported recently by the Children's Oncology Group in patients with AML treated with an intensive-timing chemotherapy regimen which showed an excellent outcome in OGS and CNS GS or because he had an inherently less aggressive AMKL, or both factors [31].

Acknowledgments

The authors thank M. Gabriela Tavera, MD (Hematology Department) and Yadira González Paredes, MD (Military General Hospital) for bibliographic support.

References

- Burns A. Observations of surgical anatomy. Head and Neck. Edinburgh: Thomas Royce & Co. 1811: 364-366. In: Neiman R, Barcos M, Berard C, et al. Cancer. 1981;48:1426-1437.
- King A. A case of chloroma. J Med. 1853;17:97. quoted by Neiman RS., Barcos M, Berard C, et al. Cancer 1981;48:1426-1437.
- Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, et al. Granulocytic Sarcoma: A clinicopathologic study of 61 biopsied cases. Cancer. 1981;48(6):1426-1437.
- Ferri E, Minotto C, Ianniello F, Cavaleri S, Armato E, Capuzzo P. Maxillo-ethmoidal chloroma in acute myeloid leukaemia: Case report. Acta Otorhinolaryngol Ital. 2005;25(3):195-199.
- Meis JM, Butler JJ, Osborne BM, Manning JT. Granulocytic sarcoma in nonleukemic patients. Cancer. 1986;58(12):2697-2709.
- Antic D, Elezovic I, Milic N, Suvajdzic N, Vidovic A, Perunicic M, et al. Is there a "gold" standard treatment for patients with isolated myeloid sarcoma? Biomed Pharmacother. 2013;67(1):72-77.
- Yamauchi K, Yasuda M. Comparison in treatments of non-leukemic granulocytic sarcoma: report of two cases and a review of 72 cases in the literature. Cancer. 2002;94(6):1739-1746.
- Menasce LP, Banerjee SS, Beckett E, Harris M. Extramedullary myeloid tumour (granulocytic sarcoma) is often misdiagnosed: a study of 26 cases. Histopathology. 1999;34(5):391-398.
- Sisack MJ, Dunsmore K, Malik NS. Granulocytic Sarcoma in the absence of myeloid leukemia. J Am Acad Dermatol. 1997;37(2 Pt 2):308-311.
- Samborska M, Derwich K, Skalska-Sadowska J, Kurzawa P, Wachowiak J. Myeloid Sarcoma in children - diagnostic and therapeutic difficulties. Contemp Oncol (Pozn). 2016;20(6):444-448.
- Yilmaz AF, Saydam G, Sahin F, Baran Y. Granulocytic sarcoma: a systematic review. Am J Blood Res. 2013;3(4):265-270.
- Dock G. Chloroma and its relation to leukemia. Am J MED Sci. 1893;106:152-157.
- Roth MJ, Medeiros LJ, Elenitoba-Johnson K, Kuchnio M, Jaffe ES, Stetler-Stevenson M, et al. Extramedullary myeloid cell tumors. An immunohistochemical study of 29 cases using routinely fixed and processed paraffin-embedded tissue sections. Arch Pathol Lab Med. 1995;119(9):790-798.
- Avni B, Koren-Michowitz M. Myeloid Sarcoma: current approach and therapeutic options. Ther Adv Hematol. 2011;2(5):309-316.
- Roby B, Drehner D, Sidmann JD. Granulocytic sarcoma of pediatric head and neck: An Institutional experience. Int J Pediatr Otorhinolaryngol. 2013;77(8):1364-1366.
- Davey FR, Olson S, Kurec AS, Eastman-Abaya R, Gottlieb AJ, D Y Mason DY. The immunophenotyping of extramedullary myeloid cell tumors in paraffin-embedded tissue sections. Am J Surg Pathol. 1988;12(9):699-707.
- Dusenbery KE, Howells WB, Arthur DC, Alonzo T, Lee JW, Kobrinsky N, et al. Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: a report from the Children's Cancer Group. J Pediatr Hematol Oncol. 2003;25(10):760-768.
- Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. Blood. 2009;114(5):937-951.
- Bassichis B, McClay J, Wiatrak B. Chloroma of the masseteric muscle. Int J Pediatr Otorhinolaryngol. 2000;53(1):57-61.
- Nayak DR, Balakrishnan R, Raj G, Pillai S, Rao L, Manohar C. Granulocytic sarcoma of the head and neck: A case report. Am J Otolaryngol. 2001;22(1):80-83.
- Lee YH, Lee NJ, Choi EJ, Kim JH. Granulocytic sarcoma (chloroma) presenting as a lateral neck mass: Initial manifestation of leukemia: a case report. Eur Arch Otorhinolaryngol. 2006;263(1):16-18.
- An SB, Cheon JE, Kim IO, Kim WS, Ahn HS, Shin HY, et al. Granulocytic sarcoma presenting with necrotic cervical lymph nodes as an initial manifestation of childhood leukaemia: imaging features. Pediatr Radiol. 2008;38(6):685-687.
- Stockl FA, Dolmetsch AM, Saornil MA, Font RL, Burnier Jr MN. Orbital granulocytic sarcoma. Br J Ophthalmol. 1997;81(12):1084-1088.
- Baldwin S, Mian A. More than meets the eye: A presentation of extramedullary infiltration (AML-M7). Clin Pediatr (Phila). 2010;49(10):986-988.
- Rojas J, Alvarez M, Suárez DV. Sarcoma granulocítico (cloroma). Pediatría. 2016;49:36-39.
- Byrd JC, Weiss RB, Arthur DC, Lawrence D, Baer MR, Davey F, et al. Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): Results from Cancer and Leukemia Group B 8461. J Clin Oncol. 1997;15(2):466-475.
- Reinhardt D, Creutzig U. Isolated myelosarcoma in children - update and review. Leuk Lymphoma. 2002;43(3):565-574.
- Brooks HW, Evans AE, Glass RM, Pang EM. Chloromas

- of the head and neck in childhood. The initial manifestation of myeloid leukemia in three patients. *Arch Otorhinolaryngol.* 1974;100(4):306–308.
29. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol.* 1995;13(7):1800–1816.
30. Uyesugi WY, Watabe J, Petermann G. Orbital and facial granulocytic sarcoma (chloroma): a case report. *Pediatr Radiol.* 2000;30(4):276–278.
31. Johnston DL, Alonzo TA, Gerbing RB, Lange BL, Woods WG. Superior outcome of pediatric acute myeloid leukemia patients with orbital and CNS myeloid sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2012;58(4):519–524.
32. Zimmerman LE, Font RL. Ophthalmologic manifestations of granulocytic sarcoma (myeloid sarcoma or chloroma). The third Pan American Association of Ophthalmology and American Journal of Ophthalmology Lecture. *Am J Ophthalmol.* 1975;80(6): 975–990.
33. Cavdar AO, Babacan E, Gozdasoglu S, Kilicturgay K, Arcasoy A, Cin S, et al. High risk subgroup of acute myelomonocytic leukemia (AMML) with orbito-ocular granulocytic sarcoma (OOGS) in Turkish children. Retrospective analysis of clinical, hematological, ultrastructural and therapeutical findings of thirty-three OOGS. *Acta Haematol.* 1989;81(2):80–85.
34. Liu PI, Ishimaru T, McGregor DH, Okada H, Steer A. Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949–1969. *Cancer.* 1973;31(4):948–955.
35. Davies JN, Owor R. Chloromatous tumours in African children in Uganda. *Br Med J.* 1965;2(5458):405–407.
36. Templeton AC. Orbital tumors in African children. *Br J Ophthalmol.* 1971;55(4):254–261.
37. Stove HK, Sandahl JD, Abrahamsson J, Asdahl PH, Forestier E, Ha SY, et al. Extramedullary leukemia in children with acute myeloid leukemia: A population-based cohort study from the Nordic Society of Pediatric Hematology and Oncology (NOPHO). *Pediatr Blood Cancer.* 2017;64(12).
38. Windebank KP, Tefferi A, Smithson WA, Li CY, Solberg Jr LA, Priest JR, et al. Acute megakaryocytic leukemia (M7) in children. *Mayo Clin Proc.* 1989;64(11):1339–1351.
39. Ribeiro RC, Oliveira MS, Fairclough D, Hurwitz C, Mirro J, Behm FG, et al. Acute megakaryoblastic leukemia in children and adolescents: a retrospective analysis of 24 cases. *Leuk Lymphoma.* 1993;10(4–5):299–306.
40. Paredes-Aguilera R, Romero-Guzmán L, López-Santiago N, Arana Trejo R. Biology, clinical, and hematologic features of acute megakaryoblastic leukemia in children. *Am J Hematol.* 2003;73(2):71–80.
41. Slavc I, Urban C, Haas OA, Kroisel PM, Köller U. Acute megakaryocytic leukemia in children. Clinical, immunologic, and cytogenetic findings in two patients. *Cancer.* 1991;68(10): 2266–2272.
42. Pui MH, Fletcher BD, Langston JW. Granulocytic sarcoma in childhood leukemia: Imaging features. *Radiology.* 1994;190(3):698–702.
43. Wendling LR, Cromwell LD, Latchaw RE. Computed tomography of intracerebral leukemic masses. *AJR Am J Roentgenol.* 1979;132(2):217–220.
44. Woo E, Yue CP, Mann KS, Ngan H. Intracerebral chloromas: unusual computed tomography appearance of leukemic infiltration. *J Comput Tomogr.* 1986;10(4):365–367.
45. Barnett MJ, Zussman WV. Granulocytic sarcoma of the brain: a case report and review of the literature. *Radiology.* 1986;160(1): 223–225.
46. Leonard KJ, Mamourian AC. MR appearance of intracranial chloromas. *AJNR Am J Neuroradiol.* 1989;10(5 Suppl):S67–S68.
47. Lu G, Altman AJ, Benn PA. Review of the cytogenetic changes in acute megakaryoblastic leukemia: One disease or several? *Cancer Genet Cytogenet.* 1993;67(2):81–89.
48. Carroll A, Civin C, Schneider N, Dahl G, Pappo A, Bowman P, et al. The t(1;22) (p13;q13) is nonrandom and restricted to infants with acute megakaryoblastic leukemia: a Pediatric Oncology Group Study. *Blood.* 1991;78(3):748–752.
49. Lion T, Haas OA, Harbott J, Bannier E, Ritterbach J, Jankovic M, et al. The translocation t(1;22)(p13;q13) is a nonrandom marker specifically associated with acute megakaryocytic leukemia in young children. *Blood.* 1992;79(12):3325–3330.
50. Bernstein J, Dastugue N, Haas OA, Harbott J, Heerema NA, Huret JL, et al. Nineteen cases of the t(1;22)(p13;q13) acute megakaryoblastic leukaemia of infants/children and a review of 39 cases: report from a t(1;22) study group. *Leukemia.* 2000;14(1):216–218.
51. Arana-Trejo RM, Paredes-Aguilera R, Nieto S, Kofman S. A t(1;22)(p13;q13) in four children with acute megakaryoblastic leukemia(M7), two with Down syndrome. *Cancer Genet Cytogenet.* 2000;120(2):160–162.
52. Gruber TA, Larson Gedman A, Zhang J, Koss CS, Marada S, Ta QH, et al. An Inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia. *Cancer Cell.* 2012;22(5):683–697.
53. Gruber TA, Downing JR. The biology of pediatric acute megakaryoblastic leukemia. *Blood.* 2015;126(8):943–949.
54. Shand JC. One giant leap for pediatric AMKL. *Blood.* 2016;127(26):3299–3300.
55. de Rooij JDE, Masetti R, Heuvel-Eibrink MMVD, Cayuela MJ, Trka J, Reinhardt D, et al. Recurrent abnormalities can be used for risk group stratification in pediatric AMKL: a retrospective intergroup study. *Blood.* 2016;127(26):3424–3430.