Granulocytic Sarcoma of The Skin Concomitant to the Diagnosis of Acute Promyelocytic Leukemia

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Sarcoma Granulocítico Cutâneo de Apresentação Concomitante ao Diagnóstico de Leucemia Promielocítica Aguda

Sarcoma Granulocitico Cutaneo de Presentacion Concomitente al Diagnostico de Leucemia Promielocitica Aguda

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ABSTRACT

Introduction: Granulocytic sarcoma (GS) is a rare extramedullary tumor, made up by immature myeloid cells. It occurs in 2% to 14% of patients with acute myeloid leukemia (AML). The association with promyelocytic leukemia (APL) is even more rare, especially as manifestation at the time of diagnosis. The present study exposes the case of a patient with cutaneous GS concomitant with a diagnosis of APL. **Case report**: Male patient, 30 years old, referred to the Hematology Department due to fever, odynophagia, intense adynamia, hyporexia, loss of 5 kg, night sweating, in addition to progressive dyspnea over one month. Laboratory exams were run with evidence of severe anemia, proceeding to etiological investigation with myelogram, which showed 84% of blasts, and immunophenotyping compatible with promyelocytic leukemia (APL), *PML-RARA* positive (90%). Also, presented ulcerated lesions in the genital region and right leg, whose biopsy showed proliferation of suspected round cells for infiltration by AML/GS. Immunohistochemistry confirmed GS. The patient underwent chemotherapy, with good response to the treatment and improvement of blood counts. Skin lesions evolved with healing. After the 3rd consolidation, *PML-RARA* was negative. **Conclusion:** This case report describes a rare presentation of a malignant hematological disease, GS, also known as skin chloroma. A diagnostic strategy including images, histopathology, immunohistochemistry and laboratory tests were needed for confirmation. Timely diagnosis is essential, so that appropriate treatment is implemented soon, benefiting the patient's survival and quality-of-life.

Key words: sarcoma, myeloid; leukemia, myeloid, acute; leukemia, promyelocytic, acute; skin neoplasms.

RESUMO

Introdução: O sarcoma granulocítico (SG) é um tumor extramedular raro, composto por células mieloides imaturas. Ocorre em 2% a 14% dos pacientes com leucemia mieloide aguda (LMA). A associação com leucemia promielocítica (LPA) é ainda mais rara, especialmente como manifestação no momento do diagnóstico. O presente estudo expõe o caso de um paciente com SG cutâneo de apresentação concomitante ao diagnóstico de LPA. **Relato do caso:** Paciente do sexo masculino, 30 anos, encaminhado ao Departamento de Hematologia por febre, odinofagia, intensa adinamia, hiporexia, perda de 5 kg, sudorese noturna, além de dispneia progressiva ao longo de um mês. Realizou exames laboratoriais com evidência de anemia grave, prosseguindo investigação etiológica com mielograma, que evidenciou 84% de blastos, e imunofenotipagem compatível com LPA, *PML-RARA* positivo (90%). Apresentava ainda lesões ulceradas em região genital e coxa direita, cuja biópsia evidenciou proliferação de células redondas suspeita para infiltração por LMA/SG. A imuno-histoquímica confirmou SG. O paciente foi submetido à quimioterapia, com boa resposta ao tratamento e melhora das contagens sanguíneas. As lesões cutâneas evoluíram com cicatrização. Após terceira consolidação, o *PML-RARA* negativou. **Conclusão:** Este relato de caso descreve uma apresentação rara de uma doença hematológica maligna, o SG, também conhecido como cloroma, na pele. Uma estratégia de diagnóstico incluindo imagens, histopatologia, imuno-histoquímica e exames laboratoriais foi necessária para confirmá-lo. O diagnóstico oportuno é essencial para que o tratamento adequado seja instituído logo, beneficiando o paciente em sobrevida e qualidade de vida.

Palavras-chave: sarcoma mieloide; leucemia mieloide aguda; leucemia promielocítica aguda; neoplasias cutâneas.

RESUMEN

Introducción: El sarcoma granulocítico (SG) es un tumor extramedular poco frecuente, compuesto por células mieloides inmaduras. Ocurre en 2% a 14% de los pacientes con leucemia mieloide aguda (AML). La asociación con leucemia promielocítica (LPA) es aún más rara, especialmente como manifestación en el momento del diagnóstico. El presente estudio expone el caso de un paciente con SG cutáneo que presenta un diagnóstico de LPA. **Relato del caso:** Paciente masculino de 30 años, remitido al Servicio de Hematología por fiebre, odinofagia, adinamia intensa, hiporexia, pérdida de 5 kg, sudoración nocturna, además de disnea progresiva a lo largo de un mes. Realizó exámenes de laboratorio con evidencia de anemia severa, continuando investigación etiológica con mielograma, que mostró 84% de blastos, e inmunofenotipificación compatible con LPA, *PML-RARA* positivo (90%). También presentaba lesiones ulceradas en región genital y muslo derecho, en las que la biopsia mostró proliferación de células redondas sospechadas para infiltración por LMA/SG. La inmunohistoquímica confirmó SG. El paciente fue sometido a quimioterapia, con buena respuesta al tratamiento y mejoría de los hemogramas. Las lesiones cutáneas evolucionaron con la curación. Después de la tercera consolidación, el *PML-RARA* fue negativo. **Conclusión:** Este reporte de caso describe una presentación poco común de una enfermedad hematológica maligna, el SG, también conocido como cloroma, en la piel. Se necesitaba una estrategia de diagnóstico que incluyera imágenes, histopatología, inmunohistoquímica y pruebas de laboratorio para confirmarlo. El diagnóstico oportuno es fundamental para que pronto se instaure el tratamiento adecuado, beneficiando al paciente en cuanto a supervivencia y calidad de vida.

Palabras clave: sarcoma mieloide; leucemia mieloide aguda; leucemia promielocítica aguda; neoplasias cutáneas.

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INTRODUCTION

Granulocytic sarcoma (GS), myeloid sarcoma or chloroma are denominations of an extramedullary tumor formed by immature myeloid cells. It can occur in bones (skull, paranasal sinuses, sternum, ribs, vertebrae and pelvis), lymph nodes, soft parts and skin more frequently and infrequently affects the Central Nervous System (CNS), orbit and genitourinary tract[1].

It affects 2% to 14% of patients with acute myeloid leukemia (AML) and occurs before, concomitantly with a diagnosis of leukemia or as an early feature of disease relapse. Also, it is found in chronic myeloid leukemia (CML) and myelodysplastic syndromes, and it is a criteria of transformation to acute leukemia. As it can occur in any organ, its diagnosis is challenging, requiring high level of suspicion; it has been associated with some morphologic alterations as myelomonocytic or monoblastic phenotype, genetic, as chromosomal translocation t(8;21) and laboratorial, as hyperleukocytosis and expression of CD56[2].

Acute promyelocytic leukemia (APL) is a subtype of AML accounting for 10%-15% of the cases, characterized by the presence of chromosomal translocation t(15;17), leading to the formation of the fusion gene *PML-RARA*. The protein coded by this chimeric gene promotes blocking of maturation and uncontrolled proliferation of promyelocytes. The most feared complication is the disseminated intravascular coagulation by hyperfibrinolysis and can cause fatal bleeding. It is treated with differentiation-inducers (all transretinoid acid – ATRA; arsenic trioxide – ATO) associated between themselves or with cytoreductive chemotherapy and eventually leading to the cure for most of the patients[3].

The association of GS with APL is rare, especially as manifestation at the diagnosis. In relapse, can be found in 3% to 5% of the patients. An increase of incidence of APL-related GS post-treatment with ATRA was detected. Two hypotheses attempt to explain this phenomenon: the first by the effect of the medication on adhesion molecules causing an increase of the infiltrative ability of leukemic cells and the second, by extended survival of the patients with the treatment. It may be related to relapse, and it is a factor of worst prognosis[4-6].

The aim of this observational, descriptive case report study is to present a case of a patient with GS of the skin concomitant with APL diagnosis. The study was conducted at "*Hospital Geral Dr. Cesar Cals de Oliveira* (HGCC)" a State reference hospital located in Fortaleza, capital of Ceará. The sample consisted in one patient hospitalized at the Hematology Department in January 2020.

Data were collected from the chart, biopsy report, other exams and photos of the lesions. The Informed Consent Form was signed voluntarily by the patient. It was approved by the Institutional Review Board (IRB) of HGCC, report number 4,527,506 (CAAE (submission for ethical review) 42724921.4.0000.5041) in compliance with Resolution 466/2012[7] of the National Health Council.

CASE REPORT

Male patient, 30 years of age, admitted to the Hematology of HGCC in January 2020 due to fever, odynophagia and purulent secretion in oropharynx during one month. He was taking amoxicillin but sought medical care due to poor results. Had unchecked fever every afternoon associated with progressive dyspnea, worsening after small efforts in 20 days. In addition, presented adynamia, hyporexia, loss of 5 kilos in one month, night sweating and neck pain. Sought care once again and lab tests revealed severe anemia (hemoglobin 3.0 g/dL), was submitted to four red blood cells concentrates transfusion and ulcerated lesions were detected in the penis and scrotum and right thigh (Figures 1 and 2).

A myelogram showed hypergranulation of blasts cells suggestive of diagnosis of APL. Immunophenotyping corroborated the morphologic diagnosis with 84% of blasts, myeloperoxidases (MPO), strong positive CD33, CD56 and CD64, weak positive CD13, further to negative HLA-DR and CD34. Karyotype by G-banding identified the t(15;17) and FISH (fluorescent hybridization *in situ* f) for *PML-RARA,* 90% rearrangement of the interphases. The biopsy of the skin lesions revealed proliferation of suspicious round cells for infiltration by AML/GS. Immunohistochemistry confirmed: focal positive CD117, focal positive anti-CD34, anti-MPO positive, anti-CD3 positive in lymphocytes T, anti-CD20 positive in lymphocytes B and anti-Ki67 positive (15%-20%).

Initiated treatment with PETHEMA[8] in January. Inductive therapy consisted in ATRA (45 mg/m²/day) until full remission, in addition to idarubicin (12 mg/m² in the 2nd, 4th, 6th and 8th days). Evolved with good response and improvement of blood counts, and post induction healing of skin lesions (Figure 3). After the third consolidation which comprehends the new cycle of ATRA and idarubicin, FISH for *PML-RARA* was negative, reaching molecular remission. No complications occurred during treatment.

DISCUSSION

The association of GS with APL is rare and becomes more rare as initial manifestation, being more common

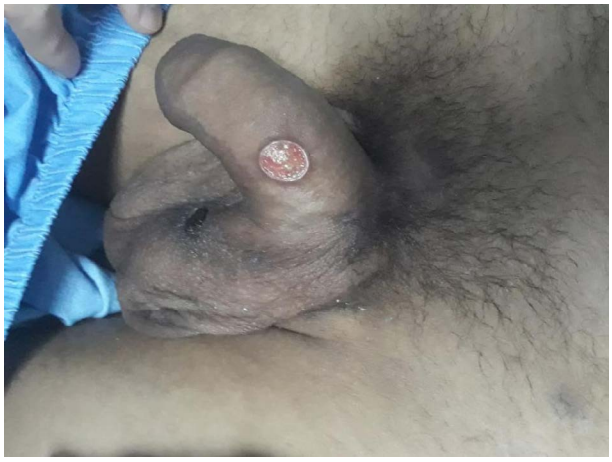

Figure 1. Ulcerated lesion in the body of penis

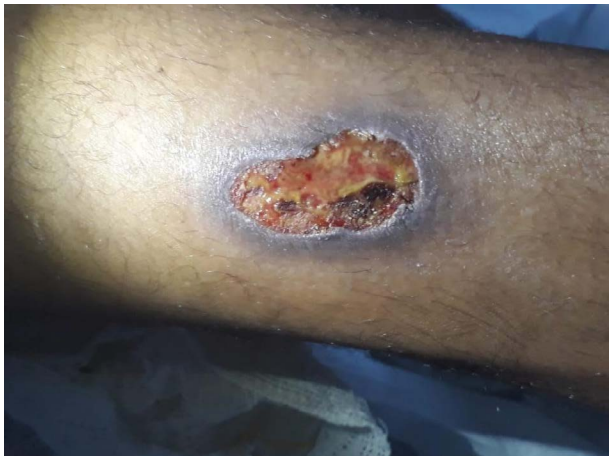

Figure 2. Ulcerated lesion in right lateral thigh

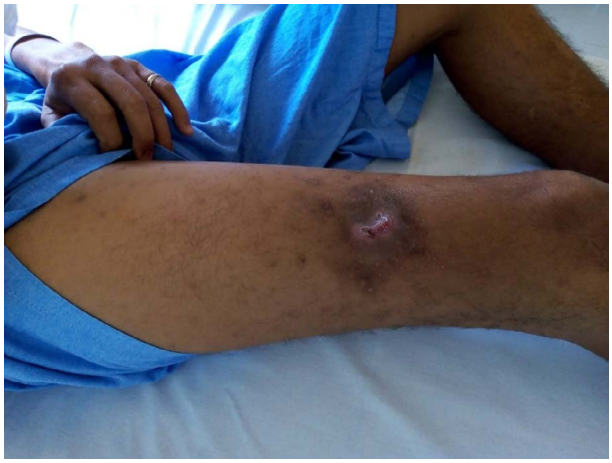

Figure 3. Ulcerated lesion in right lateral thigh in recovery

in relapses (3% to 5%)[9]. In the present case, the skin lesion was concomitant with constitutional symptoms, a triggering factor to seek medical care. GS predominates in males (1.2:1.0) and in children[10]. Yamashita et al.[11] revised 25 APL cases with extramedullary manifestation and confirmed the diagnosis in 19 males (76%); the mean age at the diagnosis was 33 years old similar to the patient investigated.

After ATRA therapy, it was noticed an increase of the incidence of myeloid tumor related to APL. For being more associated with relapse, it is considered a factor of worst prognosis. However, there are studies suggesting that the utilization of standard chemotherapy followed by hematopoietic stem-cell transplantation does not change the course of the disease[12].

GS can affect any organ, the most common are: bones, lymph nodes, soft parts and skin. A literature review found 11 cases of bone compromise (44%) followed by CNS (28%), gastrointestinal tract (12%), mediastinum and genital system (8%), skin and tongue (4%)[13]. Araújo et al.[12] evaluated 26 patients with APL and extramedullary involvement. Only in two cases (7.6%), extramedullary disease was found (pelvic mass and mandible), both with complete remission post treatment with ATRA[14].

The skin lesion usually appears as a firm papulonodular mass with accelerated growth, can be isolated, multiple or disseminated. It is locally destructive and potentially malignant. An important phase of the diagnosis is the biopsy. The cellular composition varies from a little differentiated population of blasts to mature cells, including promyelocytes and metamyelocytes, being GS classified in three categories: I – blasts; II – immature and III – differentiated. Eosinophils are visualized mainly in mature lesions[15].

Immunohistochemistry also contributed to the diagnosis. The most common marker found is CD68-KPI, in addition to KI-67/MIBI (50%-95%), MPO, CD117, CD99, CD68/PG-M1, lysozyme, CD34, terminal deoxynucleotidyl transferase, CD56, CD61, CD30, glycophorin A and CD4. Therefore, the differential diagnosis was made with lymphoblastic lymphoma, Burkitt lymphoma and diffuse of large cells B, of dendritic cells neoplasm, neuroblastoma, rhabdomyosarcoma, primitive neuroectodermal tumor and medulloblastoma. Flow cytometry distinguishes tumor with myeloid differentiation (markers CD13, CD33, CD117 and MPO) from those with monoblastic differentiation (CD14, CD163 and CD11c)[16].

The diagnosis of APL was confirmed simultaneously with skin GS. The biopsy revealed proliferation of round cells suspected of AML/GS and immunohistochemistry ratified GS. Depending on the location of the tumor, it is possible to complement the propaedeutics with imaging exams (computed tomography or magnetic nuclear resonance).

The treatment of GS includes chemotherapy, radiotherapy and surgery if tumor compression exists.

The most common chemotherapy regimen for acute leukemia is remission induction therapy. Back in 1970, it was noticed sensitiveness of APL to anthracyclines, with complete remission in more than 50% of the cases. In 1985, the revolutionary treatment ATRA was initiated to change the morbimortality with full remission in 90%. Despite the treatment, 10% of the patients evolve with relapse[11].

Yamashita et al.[11] summarized 25 cases of GS as initial manifestation of APL. Nine cases did not present medullar disease at the start. In nearly 80%, there was no coagulation abnormality at the diagnosis similar to the present study. Three patients initially were treated with ATRA, the others progressed with medullar compromise after one to 16 months[10]. Sixteen were treated with ATRA associated or not with chemotherapy with satisfactory response, however, of eight patients treated without ATRA/ATO, only three were alive at the end of the study[17]. Once the *PML-RARA* fusion gene is identified, the conduct is ATRA-based treatment.

Yamashita et al.[11] reported a case of skin lesion in a 34-years old man with medullary involvement and coagulation abnormalities at the diagnosis of APL, not treated with ATRA who survived for one month only. On its turn, Collinge et al.[9] described a case of a 49-years old woman diagnosed with APL together with abdominal skin lesion treated with ATRA and ATO, evolving to complete remission after 28 days. The patient described in the present article was treated with PETHEMA[8] and evolved with good response, improvement of blood count and healing of the skin lesions. After the third consolidation, achieved molecular remission.

The factors associated with extramedullary relapse include: younger than 45 years of age, hyperleukocytosis, microgranular morphology, expression of CD2 and/or CD56, presence of isoform BCR3 of *PML-RARA*, monotherapy without cytarabine[8]. The evolution with differentiation syndrome or ATRA syndrome is related with the development of extramedullary compromise similar to relapse.

Usually, radiotherapy has good response, but does not prevent medullary compromise when GS appears as initial presentation or avoid relapses. The time of progression to acute leukemia is greater when systemic treatment is implemented in comparison with isolated local approach (surgery or radiotherapy).

CONCLUSION

This report describes a rare presentation of a malignant hematologic disease, the skin GS. A diagnostic strategy with images, histopathology, immunohistochemistry and lab tests were necessary for confirmation. The timely diagnosis is essential to determine the correct type of treatment for improved survival and quality-of-life of the patient.

CONTRIBUTIONS

Both authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERETS

There is no conflict of interests to declare.

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None.

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