Acute myelomonocytic leukemia and leukocytoclastic vasculitis

Leucémie myéломonocytaire aiguë et vascularite leucocytoclasique

Introduction

Vasculitis is a clinical condition that may occur in association with diverse diseases, including leukemia [1-5]. The acute myelomonocytic leukemia is characterized by proliferation of neutrophilic and monocyte precursors and the finding in peripheral blood or in bone marrow of 20% or more blasts (including promonocytes); in addition to at least 20% of monocyte elements or their precursors. According to the WHO classification of 2008, there is a group of acute myeloid leukemias (AMLs) in which genetic mutations are detected, as the example of the genes FLT3-ITD or NPM1 (nucleofozmin). In adult individuals, the mutation of NPM1 gene occurs between 27 and 35% of the AMLs, and approximately 45 to 64% of them have normal karyotypes, a more frequent finding among women. Worthy of note, 80 to 90% of the cases of AMLs with NPM1 mutation, present with myelomonocyte morphology; and the classification of acute myelomonocytic leukemia is reserved for 10% of cases in which the mutated NPM1 gene is not detected. Leukemia cutis and granulocytic sarcoma are specific lesions more frequently related to acute myelomonocytic leukemia[1]. Interestingly, leukocytoclastic vasculitis can be an early manifestation or appear later in AMLs, either as a component of clinical picture, or an adverse effect of chemotherapy (CT) or other drugs [1-5].

In Brazil, the infections by Fusarium are growing in frequency among patients with leukemia and in organ transplant, but vasculitis is an exceeding rare complication in this setting [6,7]. The present case study aims to emphasize some features of non-specific skin changes associated with acute myelomonocytic leukemia, and exemplify the role of leukocytoclastic vasculitis manifestations, contributing to enhance the suspicion index about leukemia [1-5]. The increasing rate of Fusarium infections in immunosuppressed patients is highlighted [6-8].

Case report

A 75-year-old white woman had a traumatic injury on the foot one month before admission. Two weeks after, she presented with fever, asthenia, loss of appetite, and inflammatory nodules at the left inguinal region and in the anterior cervical area. Inguinal lesions evolved to ulcers with elevated borders and necrotic base (figure 1), and improved well with cephalexin. She was hypertensive, controlled by regular use of valsartan 160 mg and amlodipine 5 mg/day, and denied smoking, alcohol abuse, and other comorbidities. Physical examination revealed temperature: 36.5 °C; BMI: 30.15 kg/m²; pale skin and mucosae; heart rate: 98 bpm; blood pressure: 130/70 mmHg, respiratory rate: 20 pm; sat O₂ of 97% in ambient air; absence of visceromegaly or lymphadenopathy. Although the specimens from the ulcers only showed granulomatous tissue, and the search for microorganisms resulted negative, clindamycin and ciprofloxacin were utilized. Laboratory data on admission were hemoglobin: 6.8 g/dL, leukocytes: 12,330/mm³, blasts 18%, monocytes 36%, and platelets 27,000/mm³. Myelogram study revealed 85% of small and medium sized heterogeneous myeloblasts, some with abundant granular cytoplasm and others with scanty hypo-granular cytoplasm. The immunophenotype by flux

Figure 1

A. Ulceration observed at inguinal region on the occasion of hospital admission. B. Improved lesion in phase of cure after treatment
cytometry of bone marrow revealed 20.2% of myeloblasts (CD13, CD33, CD117, and HLA-DR positive) and 39.8% of abnormal monocytes (CD45 strong, CD33 strong, and CD4, CD11b, CD13, CD36 and CD64 positive), which are consistent findings of the phenotypic diagnosis of acute myelomonocytic leukemia. The presence of NPM1 gene mutation was considered indicative of good prognosis. Computed tomography images showed bilateral pleural effusion, atelectasis of basal segment in the right lung, and moderate pericardial effusion (figure 2A–C). The remission induction phase of her treatment was started – protocol (7 + 3) with daunorubicin 45 mg/m² (D1 to D3) and cytarabine 100 mg/m² (D1 to D7). High doses of daunorubicin were not used because of the patient age. In the aplastic phase post-CT, she evolved with febrile neutropenia, which was controlled by meropenem and vancomycin during 14 days. Six days after beginning of CT, papules and extensive erythematous-violaceous vesicles were observed in her extremities (figure 3). Because of clinical suspicion of fusariosis, voriconazole was administered during 10 days. Cultures of the lesions ruled out the presence of microorganisms and the histopathology findings established the diagnosis of leukocytoclastic vasculitis (figure 4). Ultrasonography with Doppler showed pervious vessels in the extremities, and there was an increased echogenicity of the subcutaneous tissue related to local edema. Magnetic resonance images revealed an area partially delimited of hypersignal in T2, and discrete hyper signal in T1 on the volar face of the proximal phalange of the right fifth finger, next to the flexor tendon (figure 2D) with extension of $16 \times 11 \times 10$ mm. There was no contrast enhancement, and the rest of structures were unremarkable. The myelogram of control performed three days before the hospital discharge confirmed the complete remission after the induction, with only 1% of residual myeloblasts and absence of monocyte elements. With clinical and laboratory improvement, the patient was discharged on the Day 30 of hospitalization. Furthermore, she underwent a successful consolidation phase of treatment with high-dose Ara-C, in other Oncohematologic service. Currently, she is regularly under periodical specialized follow-up, and persists asymptomatic with normal general clinical parameters.

Discussion
A case study of leukocytoclastic vasculitis is described in an old woman with acute myelomonocytic leukemia, who presented with two varieties of cutaneous lesions. Initially, ulcerated nodes probably associated with an antecedent trauma in her foot. Posteriorly, papules and vesicles appeared in the extremities, raising the non-confirmed hypothesis of infection by Fusarium. Furthermore, the diagnosis of leukocytoclastic vasculitis was confirmed with base on histopathological data. In the small dermal vessels, there was transmural neutrophilic infiltrate, fragmentation of leukocytes, endothelial edema, solution of wall vessel continuity, and fibrinous necrosis [4]. Although the search for microorganisms had been negative, she was treated with voriconazole, which is considered a less nephrotoxic therapeutic option if compared with the classical utilization of Amphotericin B [8]. Clinical and laboratory responses to CT were successful, and the changes of vasculitis remitted during the post aplasia phase of bone marrow recuperation, without specific immunosuppression. Vasculitis is classified as primary or idiopathic, and secondary to diverse conditions [4]. Leukocytoclastic vasculitis has been related to autoimmune disorders, infections, adverse drug-reactions, and more rarely to malignancies, in special lymphomas and leukemias [1–5]. Interestingly, the cutaneous lesions may appear as isolated events, or in recurrent episodes [4]. Tzavara et al. described a facial exanthema similar to heliotrope of dermatomyositis [5], and the
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Figure 3
A to C. Computed tomography images of the thorax showing bilateral pleural effusion and segmental atelectasis on the right lung base, in addition to inspissation and small pericardial effusion. D. Magnetic resonance of the right hand, revealing area of hypersignal in T2 at volar face of the proximal phalange of the fifth finger, without contrast enhancement.

Figure 4
Photomicrography of specimens from the skin biopsy performed on the hand dorsum. A. The horny layer presents preserved and reticulated; in the epidermis, there is discrete acanthosis and spongiosis, vacuolization of the basal layer and some necrotic keratinocytes (HE, × 40). B to D. In the superficial derma there is degeneration of collagen fibers and vasculitis of small venules, with predominant neutrophils and presence of their fragments, in addition to fibrin deposition (HE, × 100).
patient herein reported presented a maculo-papular lesion in the proximity of the ear. Vasculitis occurs in up to 8% of malignancies, with leukocytoclastic features in 45% of cases [4]. Skin changes of vasculitis may be variable, and can be initial manifestation of leukemia [1-5]. Aspergillosis and fusariosis are the more common mycoses in immunosuppressed patients [6]. Pulmonary and pericardial involvement similar to those of the present report may occur in patients with acute leukemia; moreover, these changes also mimicked lesions described in individuals with disseminated fusariosis acquired by skin or airborne inoculations [6]. Differential diagnosis with fungal infections should be established and, if not completely clarified, empirical treatment for fusariosis must be initiated as soon as possible.

Conclusion
According to the WHO classification (2008), the patient was diagnosed with AML with recurrent genetic abnormalities, subgroup with NPM1 mutation [9,10]; and by FAB classification this was the AML-M5 type - acute myelomonocytic leukemia. Lesions of leukocytoclastic vasculitis appeared after starting CT, probably due to drug side effects. These changes may precede, concur or follow manifestations of leukemia. Differential diagnosis with infection by filamentous fungi was justified by the growing number of these conditions in our country.

Disclosure of interest: the authors declare that they have no competing interest.

References

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