Clinical Case Report

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Case report: Purulent transformation of granulocytic sarcoma

An unusual pattern of differentiation in acute promyelocytic leukemia

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Abstract

Rationale: Acute promyelocytic leukemia (APL) is a curable subtype of acute myeloid leukemia. APL is currently treated with combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) resulting in the induction of apoptosis and differentiation of the leukemic cells. Differentiation syndrome (so-called ATRA syndrome) is the main life-threatening complication of induction therapy with these differentiating agents.

Patient concerns: Herein, we report the case of a 49-year-old woman diagnosed with APL with, concomitantly, a bulky cutaneous lesion of 10 cm diameter with a red-to-purple background and a necrotic center, localized on her abdomen.

Diagnoses: After 10 days of treatment, the cutaneous lesion became purulent. Fluorescence in situ hybridization (FISH) analysis performed on this pus confirmed the presence of malignant features in the involved granulocytes proving their origin from the differentiation of leukemic APL cells, as all the analyzed nuclei showed 2 promyelocytic leukemia (PML)–retinoic acid receptor-a (RARA) fusions signals.

Intervention: The association by ATRA and ATO was continued.

Outcome: Eventually, the evolution was favorable with healing in three weeks.

Lessons: This case report therefore highlights the differentiation phenomenon of promyelocytic blasts within promyelocytic sarcoma with the ATRA–ATO combination and the efficacy of this drug association in resolving both the malignant sarcoma and a secondary local infection.

Abbreviations: AML = acute myeloid leukemia, APL = acute promyelocytic leukemia, ATO = arsenic trioxide, ATRA = all-trans retinoic acid, CR = complete remission, FISH = fluorescence in situ hybridization, SIRS = systemic inflammatory response syndrome.

Keywords: acute promyelocytic leukemia, chloroma, differentiation

1. Introduction

Acute promyelocytic leukemia (APL) is a curable subtype of acute myeloid leukemia (AML). It represents 10% to 15% of all adult AML cases.[1–4] APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, which generates a fusion transcript joining the PML (*promyelocytic leukemia*) and RARA (*retinoic acid receptor-α*) genes.[1,4,5] The chimeric protein causes a blockade of differentiation and increases self-renewal of leukemic progenitor cells.[3,4]

Initially only treated by chemotherapy regimens, APL is currently curable with chemo-free treatments combining all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).[2,6,7] These agents target the PML–RARA oncoprotein through distinct mechanisms, resulting in the induction of apoptosis and differentiation of the leukemic cells.

Differentiation syndrome (so-called ATRA syndrome) is the main life-threatening complication of induction therapy with these differentiating agents. The pathogenesis seems to be based on a systemic inflammatory response syndrome (SIRS) mediated by cytokines released from differentiating malignant cells, endothelium damage with capillary leak syndrome, occlusion of microcirculation, and tissue infiltration.[8]

Herein, we report a case in which APL was associated with a cutaneous promyelocytic sarcoma evolving under therapy to a purulent transformation in relationship with a mechanism of cell differentiation.

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Key Points: A woman with acute promyelocytic leukemia and promyelocytic sarcoma recovered after treatment by differentiating agents and purulent evolution within the extramedullary lesion.

The patient gave her informed consent for publication.

The authors have no conflicts of interest to disclose.

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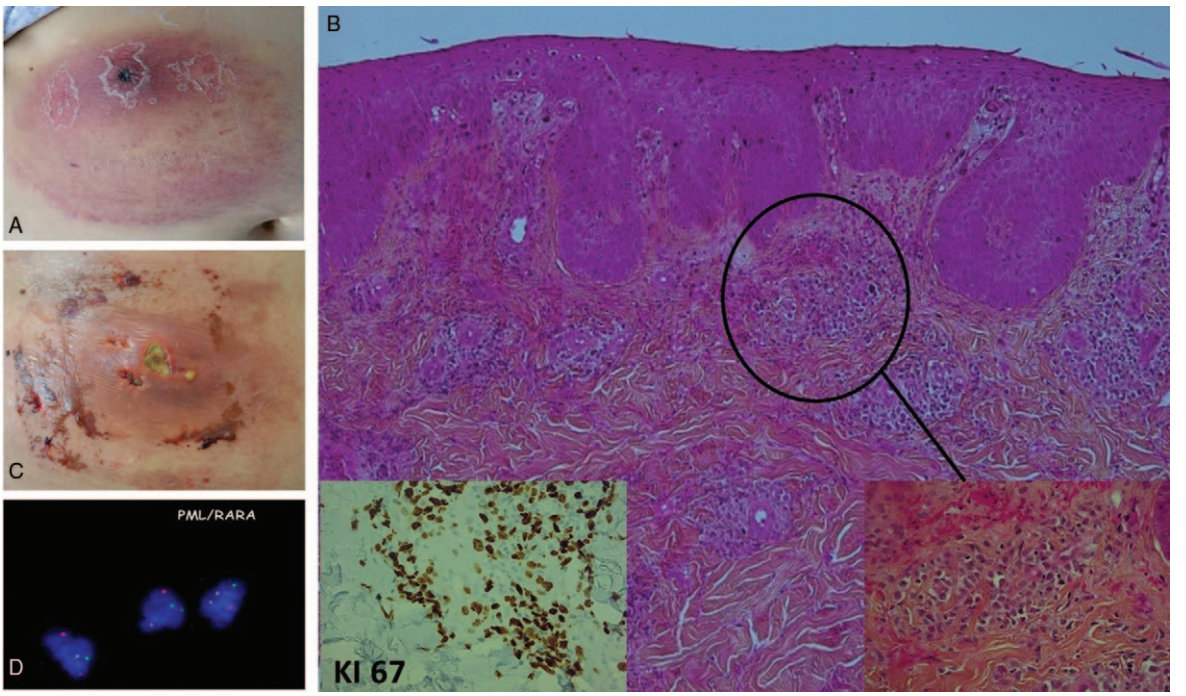

Figure 1. (A) Abdominal cutaneous lesion at diagnosis cutaneous lesion with a purple background and a necrotic center. (B) Histological analysis of the cutaneous biopsy revealing a granulocytic sarcoma with a pericapillar infiltrate in APL. (C) Purulent evolution of the cutaneous lesion during the treatment associating transretinoic acid and arsenic trioxide. (D) FISH analysis performed on cells from the pus demonstrated PML/RARA fusion illustrating the differentiation syndrome.

2. Case description

A 49-year-old woman was diagnosed with APL on February 2017. She presented in a context of spontaneous multiple hematomas and fever. Initial peripheral blood count showed hyperleukocytosis (20 G/L) including 90% of leukemic blasts cells containing Auer rods, anemia, neutropenia, and thrombocytopenia, associated with initial signs of coagulopathy. Bone marrow aspirates confirmed a marrow infiltration by 80% of promyelocytic blasts. The translocation (15;17) was detected by cytogenetic and the presence of a PML–RARA fusion transcript (bcr1) was confirmed by RT-PCR.

Concomitantly, the patient presented a bulky cutaneous lesion of 10 cm diameter with a red-to-purple background and a necrotic center, localized on her abdomen (Fig. 1A). The histological analysis revealed the presence of cells expressing myeloperoxidase, CD68, and CD163. The cutaneous biopsy showed an extramedullary localization with APL cells displaying a high KI-67 expression (Fig. 1B) and therefore confirmed a diagnosis of promyelocytic sarcoma.

After an initial cytoreduction by hydroxycarbamide, a treatment combining ATRA (45 mg/m^2/day) with ATO (0.15 mg/kg/day) was initiated according to the schedule recently published by Lo-Coco et al.[2]

After 10 days of treatment, a discharge of pus appeared at the center of the cutaneous lesion (Fig. 1C). Fluorescence in situ hybridization (FISH) analysis performed on this pus confirmed the presence of malignant features in the involved granulocytes proving their origin from the differentiation of leukemic APL cells, as all the analyzed nuclei showed 2 PML–RARA fusions signals (Fig. 1D). Bacterial culture remained sterile although no antibiotic therapy was introduced. The local evolution was spontaneously favorable by 3 weeks. No signs of differentiation syndrome were noted. Complete remission (CR) was achieved by day 28, with a reduction of PML–RARA/ABL1 up to 0.008%.

The patient received continuation therapy with ATO consolidations as previously described.[2] She is still in molecular remission with no evidence of promyelocytic sarcoma after a 6-month follow-up.

3. Discussion

We present here an unusual case of APL. To our knowledge, this is the first case demonstrating the involvement of leukemic cells in the purulent evolution of a cutaneous promyelocytic sarcoma. Extramedullary disease has been associated with every cytologic French-American-British (FAB) AML subsets, and has been seldom found with APL. In this AML subtype, skin and central nervous system (CNS) are the preferential sites of extramedullary involvement. As a proportion of patients never develop systemic disease, correct and timely diagnosis may be rather difficult. This was not the case in the present report since cutaneous promyelocytic sarcoma occurred concomitantly to leukemic blood and marrow involvement. The cutaneous biopsy was performed despite the highly inflammatory skin lesion yielding to confirm the diagnosis. Although the occurrence of extramedullary localization has increasingly been reported in APL since the introduction of ATRA therapy[9] and has suggested a relationship with its direct effect on adhesion molecules resulting in increased infiltration capability of blastic cells,[10] the effect of ATRA (as that of ATO) does not seem to be involved here since the cutaneous lesion was present before the initiation of therapy. The occurrence of the ATRA syndrome has also been recognized to be a significant risk factor for extramedullary involvement, especially at relapse.[10] However, manifestations of ATRA syndrome were not demonstrated in our case report and the cutaneous lesion occurred before the initiation of any therapy.

Since the end of the 1980s, standard treatment in APL consisted of the combination of ATRA with conventional chemotherapy. This has also represented the treatment of APL with extramedullary localizations potentially combined with complementary local radiotherapy and consolidation reinforcement by allogeneic stem cell transplantation. In our case report, treatment was only based on the chemo-free schedule recently proposed for APL therapy.[2] Although the follow-up was still short, this tend to confirm the potential efficacy of the combination ATRA–ATO on promyelocytic sarcoma since no relapse occurred after a 6-month CR duration.

Actually, this unusual observation mainly stresses on the purulent evolution of the promyelocytic sarcoma in relationship with the differentiation of leukemic blasts into mature neutrophils, as demonstrated by FISH analysis performed on altered neutrophils forming the pus. Promyelocytic blasts differentiated under the effect of ATRA and ATO within the cutaneous sarcoma similarly to what was observed on peripheral blood smears showing mature neutrophils containing Auer rods. Despite any signs of systemic or local infection and any identification of bacteria, the occurrence of pus signed an infectious participation into the inflammatory cutaneous lesion. Our case report therefore highlights the differentiation phenomenon of promyelocytic blasts within promyelocytic sarcoma with the ATRA–ATO combination and the efficacy of this drug association in resolving both the malignant sarcoma and a secondary local infection. Differentiated leukemic cells appeared as able to fight bacteria and to be still efficient on a local infection, suggesting also a potential participation in limiting systemic or more severe infections. This brings further arguments in favor of the use of differentiating drug combination over the use of a combination involving cytotoxic chemotherapy for the treatment of APL.

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