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case of the month

Cutaneous promyelocytic sarcoma at sites of vascular access and marrow aspiration. A characteristic localization of chloromas in acute promyelocytic leukemia?

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ABSTRACT

Extramedullary disease (EMD) is a rare clinical event in acute promyelocytic leukemia (APL). Although the skin is involved in half of the reported EMD cases, the occurrence of cutaneous promyelocytic sarcoma (PS) has been described very rarely. We report here three cases of PS which have the peculiarity of appearing at sites of punctures for arterial and venous blood and marrow samples (sternal manubrium, antecubital fossa, wrist over the radial artery pulse, catheter insertion scar). At presentation, all patients had hyperleukocytosis and a morphologic diagnosis of microgranular acute promyelocytic leukemia variant confirmed at the genetic level by demonstration of the specific chromosomal translocation t(15;17). A BCR3 type PML/RARα transcript was documented in the two patients for whom diagnostic RT-PCR was available. Patients had morphologic bone marrow remission at the time the PS appeared. A predilection for the development of cutaneous PS at sites of previous vascular damage has been noted, but the pathogenesis remains largely unknown. A potential role for all-trans retinoic acid has been advocated, although one of the three patients in our series had received no ATRA. A review of the literature revealed six similar cases and hyperleukocytosis at diagnosis was a consistent finding in all of them. A careful physical examination of these particular sites in the follow-up of patients at risk, as well as cutaneous biopsy and laboratory examination of suspected lesions are strongly recommended.

Key words: acute promyelocytic leukemia, granulocytic sarcoma, promyelocytic sarcoma

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In patients with acute promyelocytic leukemia (APL), extramedullary disease (EMD) is a very rare clinical event, the skin being the most commonly affected site. In fact, the skin is involved in half of the reported cases of EMD,[1,2] while the disease is equally distributed among the other sites: central nervous system (CNS), gingiva, bone, lymph nodes, spleen, etc.

Several types of leukemic infiltrates (leukemia cutis) have been reported in APL patients. As in other acute myeloid leukemias (AML), such cutaneous lesions may appear as multiple papules, nodules, infiltrated plaques and macules. Although uncommon, a pathognomonic lesion of AML that can also develop in the skin is chloroma, more appropriately termed granulocytic sarcoma (GS) or promyelocytic sarcoma (PS) when it occurs in APL. Leukemia cutis in AML has been known to localize at sites of trauma, burns, intramuscular injections, herpes and scars, including Hickman catheter sites.[3] Although this particular preference has not been previously noted for leukemia cutis in APL, we hypothesize that this special AML subtype could have a preferential localization of PS in the skin at sites of vascular disruption, such as punctures for arterial and venous blood and marrow samples (wrist overlying the radial artery pulse, antecubital fossa and sternal manubrium), as well as catheter insertion scars. In fact, of 128 consecutive APL patients diagnosed at our Institution, the only three cases who had leukemic infiltration of the skin showed various subcutaneous PS coinciding with the aforementioned sites. In all three cases, PS were localized at the site of a previous indwelling central venous catheter insertion, or where arterial or venous blood had previously been taken (radial artery pulse, antecubital fossa) or bone marrow aspirated (sternal manubrium). This phenomenon has not been noted in 11 patients with granulocytic sarcoma (GS) recorded at our institution from a series of 763 patients with non-promyelocytic AML. In addition, after a review of the reported cases of cutaneous involvement in APL patients (Table 1), we realized that most of the compatible descriptions of PS, like the cases reported here, had occurred at the insertion site of a permanent indwelling central venous catheter,[4,7,10] sites of venipuncture[1,4,7,18] or bone marrow aspiration.[12]

Table 1. Reported cases of leukemic skin involvement in APL.

Author (Case #)	*Year*	*Age*	*Sex*	*WBC x10⁹/L*	*t(15;17)/ PML/RARα*	*CD13/ CD56*	*Time from diagnosis (mo.)*	*ATRA*	*Description of cutaneous involvement*
Bernego[4]	*1975*	*82*	*M*	*NA*	*NA*	*NA/NA*	-	*No*	*Nodules in antecubital fossa and in subclavian cathether*
Matsumoto[5]	1978	21	F	NA	NA	NA/NA	NA	No	Nodules in chest, back and breast
Baer[6] (#13)	1989	59	F	NA	NA	NA/NA	36	No	Single large lesion on back
Niazi[7] (#1)	*1991*	*26*	*M*	*NA*	*NA*	*NA/NA*	*NA*	*No*	*Nodules at insertion site of subclavian catheter and antecubital fossa*
Longracre[8]	1993	19	M	NA	Yes	NA/NA	NA	NA	Two lesions (?). Extensive dermal infiltrate with epidermotropism
Giralt[9] (#2)	1994	35	M	26	Yes	NA/NA	1.5	Yes	Four papular lesions (0.5-1 cm) in the left thigh
Giralt[9] (#3)	1994	47	F	NA	NA	NA/NA	5	Yes	Infiltrative plaques and papules on her forehead and eyelids
Giralt[9] (#1)	1994	23	M	35	Yes	NA/NA	13	Yes	Three violaceous skin nodules (1 cm) on the scalp
Thomas[10]	*1994*	*68*	*F*	*35*	*Yes*	*NA/NA*	*10*	*Yes*	*Three subcutaneous nodules (1-3 cm) on the route of the former intravenous catheter*
Weiss[11] (#1)	1994	31	M	NA	Yes	+/NA	11	Yes	A 0.4 cm exophytic lesion in external auditory canal
Weiss[11] (#2)	1994	33	M	NA	Yes	+/NA	11	Yes	Lower extremity rash, manifested as erythematous plaques with raised borders
Békássy[12]	*1995*	*24*	*F*	*NA*	*NA*	*NA/NA*	*NA*	*NA*	*Presternal skin*
Lederman[13]	1995	46	F	NA	Yes	NA/NA	6	No	Subcutaneous nodules on right lower abdomen and left flank
Wiernik[1] (#2)	*1996*	*25*	*F*	*76*	*Yes*	+	*6*	*No*	*Subcutaneous nodule (1x1 cm) in antecubital fossa*
Selleri[14]	1996	31	F	NA	Yes	NA/NA	18	No	21 palpable skin nodules (0.5-1.5 cm) on her trunk
Ueda[15]	1997	66	M	17	Yes		8	Yes	Multiple scattered, red to brown, 3 to 5 mm, discrete and confluent papules on trunk
Del Río[16]	1997	28	F	40.1	NA	+/NA	7	N	Small groups of greyish-green papules of 0.5 cm on (?) and on lumbar region
Kishimoto[17]	1997	11	F	2.6	Yes	NA/-	2	Yes	Multiple cutaneous nodules with hyperpigmentation developed in the anterior trunk
Kumar[18] (#6)	*1997*	*22*	*F*	*NA*	*No*	*NA/NA*	*5*	*NA*	*Skin nodules in right forearm (3.5 cm)*
Nagao[19]	1997	30	F	26.1	No	+/NA	12	Yes	Reddish purple nodules up to 1 cm and subcutaneous tumor mainly on the extremities
Bobbio[20]	1998	NA	M	NA	Yes	NA/NA	-	Yes	Two green masses in the fronto-parietal scalp and in the lumbar region
Liso[2]	1998	22	F	39.8	Yes	+/+	18	No	A single purplish skin lesion in sacral region
Liso[2] (#2)	1998	48	M	18	Yes	+/-	14	No	Multiple erythematous skin lesions, featuring brownish-red papules (2-3 cm in greatest dimension) on the back and abdomen
Liso[2] (#4)	1998	25	F	3.2	Yes	+/-	12	No	Multiple large raised skin lesions (3 cm in greatest dimension) on the anterior and posterior thoracic regions, the neck and the abdomen
Liso[2] (#6)	1998	44	F	4	Yes	+/-	14	Yes	13 purplish-red tender skin lesions (0.5 in greatest dimension) in the abdomen
Liso[2] (#7)	1998	45	M	10.4	Yes	+/-	-	Yes	Rash featuring multiple erythematous plaques with raised borders and hyperpigmentation
Milone[21]	1999	41	M	NA	Yes	NA/NA	69	Yes	Cutaneous nodules

NA denotes "not available"; cases with compatible description of cutaneous PS at sites of vascular disruption are in italics.

Case Reports

Case #1

In April 1983, a 55-year old man presented with a WBC of 118×10⁹/L. APL was morphologically suspected (bone marrow was hypercellular with 96% hypogranular promyelocytes) and later confirmed by demonstration of the t(15;17). A diagnosis of microgranular APL (M3v) was established. He received induction chemotherapy with daunorubicin (2 mg/kg/d×5 days), achieved complete remission (CR) and was given polychemotherapy consolidation. Seven months after diagnosis he complained of the appearance of a subcutaneous nodule at the sternal manubrium. Physical examination also found two other subcutaneous nodules on his right wrist overlying the radial artery pulse, where punctures for blood gases had been performed, and at the site of the intravenous catheter scar (Figure 1). The skin biopsy showed a characteristic PS. Forty days later, while the patient was on a waiting list for radiation therapy, bone marrow relapse was detected and a new induction treatment was administered. The patient died of cerebral hemorrhage and pulmonary edema on day 43 after the initiation of salvage chemotherapy.

Case #2

A 28-year old man was diagnosed as having t(15;17)-positive APL in June 1996. On admission, his WBC was 79.8×10⁹/L. The bone marrow was infiltrated by 98% hypogranular promyelocytes consistent with a diagnosis of microgranular APL (M3v). Immunophenotyping revealed that virtually all bone marrow cells were HLA-DR⁻, CD13⁺, CD33⁺ and CD34⁻, CD2⁻, CD9⁻, CD16⁻. A PML/RARα hybrid mRNA (BCR3 type) was demonstrated by RT-PCR. He received daunorubicin (60 mg/m²/d × 3 days) and cytarabine (200 mg/m²/d × 7 days) plus ATRA (45 mg/m²/d until remission). In the postchemotherapy period the patient developed severe respiratory failure with recurrent pleural effusions that required a prolonged admission in the critical care unit. Bone marrow examination on day +33 showed hematologic complete remission. In October 1996, he received a first consolidation cycle of chemotherapy (daunorubicin + cytarabine) without complications. Six months after diagnosis, several painless subcutaneous nodules appeared simultaneously at the jugular catheter scar, at both wrists at the level of the radial artery pulse, and at the sternal manubrium. A

Figure 1. Promyelocytic sarcoma at catheter insertion site and sternal manubrium.

bone marrow tap showed no morphologic evidence of leukemic infiltration, but presence of residual PML/RARα transcript was demonstrated by RT-PCR. The biopsy of nodules showed typical features of PS. Intensive chemotherapy followed by local radiotherapy was started but the skin nodules were unresponsive to treatment. The patient died during post-chemotherapy aplasia due to *Aspergillus* pneumonia.

Case #3

A 14-year old girl, who presented with fever, spontaneous gingival and cutaneous bleeding, was admitted to hospital in June 1996. Her initial WBC count was 20.7×10^9/L with 90% blasts. Flow cytometry revealed that more that 80% of the leukemic cells were HLA-DR$^-$, CD13$^+$, CD33$^+$, CD34$^+$, CD2$^+$, CD9$^+$, CD16$^-$ and CD56$^-$. Morphologic diagnosis of microgranular APL variant was confirmed by the presence of the t(15;17) and by RT-PCR amplification of a BCR3 type PML/RARα rearrangement. The girl received daunorubicin (60 mg/m^2/day × 3 days) and cytarabine (200 mg/m^2/day × 7 days) plus ATRA (25 mg/m^2/day until remission). A bone marrow examination on day +37 showed hematologic complete remission. The patient received two consolidation courses with daunorubicin and cytarabine and maintenance with ATRA for two years according to the APL-93 protocol of the European APL group.[22] In February 1999, 3 months after the end of therapy and 32 months after diagnosis, she displayed two elevated painless nodules on the sternal manubrium (3×2 cm) and in her left antecubital fossa (1×1cm). Fine needle aspiration of the nodules revealed atypical promyelocytes displaying the typical microspeckled pattern by immunostaining with an anti-PML monoclonal antibody (PGM3).[23] Bone marrow aspirate showed hematologic and molecular remission. In addition to external-beam radiation therapy to both nodules, which leds to their disappearance, maintenance therapy was restarted with ATRA, mercaptopurine and methotrexate as described elsewhere.[22] At present, 5 months after radiation therapy for cutaneous relapse, the patient remains in complete remission.

Discussion

EMD, and particularly cutaneous infiltration, apart from being extremely infrequent in APL, is not a characteristic of this particular subtype of AML. Central nervous system (CNS) involvement and leukemia cutis are more common in other subtypes of AML, particularly those with a monocytic component (M4 and M5),[24] and along with GS are frequently associated with t(8;21)-positive AML.[25] Nevertheless, the experience reported here, as well as a review of the literature suggests that, besides its rarity, cutaneous PS in APL has a characteristic predilection to emerge in skin sites where vascular disruption occurred during the active phase of the disease. In fact, following the presently reported observations on our patients, we carefully reviewed the literature on cutaneous infiltration in APL (Table 1) and recognized some cases with striking similarities to the cases we described (Table 2).[4,7,10,12,18] In contrast, although leukemia cutis has been known to localize at sites of trauma, burns, intramuscular injections and recent surgery, including Hickman catheter sites,[3] among 763 patients diagnosed as having AML at our institution during the same period, none of 11 cases of GS was localized to the site of vascular punctures or bone marrow aspiration.

The apparent predilection for the development of PS at sites of insertion of an indwelling central venous catheter, and in sites of previous punctures for venous and arterial blood samples and for bone marrow aspiration, is noteworthy. As a possible explanation, we hypothesize that a major disruption of the wall of blood vessels with secondary large bleeding into the skin would constitute a first step required for the creation of a leukemic cell "sanctuary". The leakage of sufficient amounts of soluble growth factors and cell

Table 2. Present study cases of cutaneous promyelocytic sarcoma.

Case #	*Year*	*Age (years)*	*Sex*	*WBC x10^9/L*	*t(15;17)/ PML/RARα*	*CD13/ CD56*	*Time from diagnosis (mo.)*	*ATRA*	*Description of cutaneous involvement*
Case #1	1983	55	M	118	Yes	ND	7	No	Nodules at catheter insertion site, radial artery pulse and sternal manubrium.
Case #2	1996	28	M	79.8	Yes	+/ND	6	Yes	Nodules at catheter insertion site, radial artery pulse and sternal manubrium.
Case #3	1996	14	F	20.7	Yes	+/-	32	Yes	Nodules at antecubital fossa and sternal manubrium.

mediators into subcutaneous tissue would lead to a protected environment in which viable atypical promyelocytes could survive and proliferate. In contrast, minor capillary bleeding most commonly seen in APL would not be sufficient to provide an adequate microenvironment for survival of malignant cells. However, because EMD is extremely rare and bleeding is a very common complication of APL, the above interpretation might be too simplistic. Alternatively, specific properties and characteristics of atypical promyelocytes might be present in some cases which would favor the development of PS. CD56 expression in diagnostic cells has been related to the formation of GS in other subtypes of AML,[26,27] and associated with multidrug resistance and a poorer outcome in patients with t(8;21) AML. Although the expression of CD56 in APL is very rare, and its significance is uncertain, no relationship with the appearance of PS has so far been reported.[28] In the present series, only one patient was studied for CD56 expression and tested negative (case #3). The expression of other adhesion molecules on the surface of atypical promyelocytes could also be relevant, although the incidence and significance of these remain to be established. For example, the expression of certain adhesion molecules, such as aminopeptidase N (CD13) has been associated with tumor invasive capacity in some human cell lines,[29] and with extramedullary leukemic infiltration of APL.[1] All cases reported after those reviewed by Wiernik *et al.*,[1] in which data on CD13 were available, tested positive for this molecule,[2,16,19] including two patients of the current study (cases #2 and #3). Another common feature we found associated with the appearance of PS was hyperleukocytosis, which was also a recurrent feature in cases reported in the literature.[1,10] Hyperleukocytosis has been well recognized as the most important relapse risk factor in APL.[22,30-32] This finding is clearly associated with the variant M3 morphology observed in every case, as well as the BCR3 type of PML/RARα transcript, which was documented in the two cases in which diagnostic RT-PCR was available.

Interestingly, the vast majority of EMD cases, and especially those with cutaneous involvement, has been reported following the introduction of ATRA in the treatment of APL, leading to speculation on the potential role of this drug in the increasing incidence of EMD in APL patients.[1,2,9,11] As a first hypothesis, it should be considered that the better survival of patients receiving ATRA-containing protocols[33,34] would increase the number of cases and the time at risk to develop EMD. In our study, two patients (cases #2 and #3) were part of the group of 41 patients who achieved CR with several protocols combining ATRA and chemotherapy in the last nine years,[22,30,33] while the remaining one (case #1) belongs to the group of 41 CR obtained in the pre-ATRA era.[35] Alternatively, ATRA has been shown to have a direct effect on APL blasts through modulation of adhesion molecules. In fact, ATRA-induced differentiation is followed by changes in the expression pattern of molecules that enhance adherence properties of APL cells.[36]

EMD in patients with APL has been also related to certain ethnic groups and to the administration of growth factors.[1] None of our patients reported herein had been treated with hematopoietic growth factors. Awareness of the potential predilection for cutaneous GS development in APL should contribute to better recognition of new cases, as well as to the investigation and clarification of the pathogenetic mechanisms and risk factors involved in this odd phenomenon.

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All authors participated in designing the study and writing the paper. The order of authorship takes into account the scientific contribution given to the study.

Disclosures

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