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LETTER TO THE EDITOR

Intravascular Occlusion by Leukemic Blast Cells Causing Multiplex Hand Necrosis in a Patient with Acute Myeloid Leukemia

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In April 2017, a 76 years old female patient with a history of hypertension, hypothyreosis and left renal artery stenosis was diagnosed with acute myeloid leukemia (AML; FAB M4). She presented with poor prognostic markers including complex karyotype with wild-type FLT-3 and NPM-1 mutations. After induction chemotherapy (3 + 7 regimen, consisting 60 mg/m^2 of daunorubicin and 100 mg/m^2 of cytosine arabinoside) she experienced treatment failure with progressive disease and newly detected peripheral blast cells. After receiving dismal results she withdrew consent for further treatment.

In May 2018 she presented at the Hematology Division with severe anemia (5.3 g/dl), thrombocytopenia (22×10^9/L) and normal leukocyte count (7.1×10^9/L). The original, myelomonocytic blast cells were identified on the peripheral blood smear (30%). Considering the patient's age and withdrawal of consent for high dose chemotherapy, we initiated treatment with azacitidine (75 mg/m^2/day for 7 days). Two weeks after completion of the first cycle of azacitidine, the patient was admitted to our ward with a 24-h history of sudden-onset pain and bruising in her right middle finger and left thenar eminence (Panel A, Image 1).

Arterial and venous Doppler ultrasonography showed normal findings. Bacterial embolization was excluded based on the results of several negative hemocultures and transesophageal echocardiography. Fine needle aspiration cytology cultures, taken from the affected areas were also negative. Viral serology testing did not confirm any viral infection. Thromboembolisation was not likely, considering the severe thrombocytopenia with normal coagulation profile, D-dimer and FXIII levels. Immunological testing revealed normal ranges of anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibody (ANA) and anti-extractable nuclear antibody (ENA) and was negative for cryoglobulins.

Taking the aforementioned results into consideration, differential diagnosis included extramedullary disease, vasculitis, a severe manifestation of Achenbach's syndrome [1], and direct occlusion of small vessels by circulating blast cells. Despite receiving best supportive care available (including empiric antibacterial, antifungal and antiviral therapy, hemosupportation, hydroxyurea, β-receptor agonists, pentoxyphyllin and alprostapint), our patient experienced rapid progression to skin necrosis and underwent surgical necrectomy of the left palmar lesion and amputation of the distal phalanx of the right middle finger (Panel B). Histopathological evaluation of the resected phalanx revealed direct occlusion of small vessels via leukemic blast cells, resulting in diffuse ischemic necrosis of the skin (Panel D). After the procedure, technetium-99 m hand perfusion scintigraphy confirmed the disturbance of microcirculation in both hands (Panel E).

With several new skin lesions appearing on both hands of our patient, after receiving informed consent, we started combination of hydroxyurea in an elevated dose (30 mg/kg/day, continuously) and cytosine arabinoside (20 mg/m^2/day for 5 days) with cytoreductive intent. Rapid cytoreduction via cytotoxic chemotherapy was highly effective: peripheral blast count decreased while new skin lesions regressed and surgical wounds started healing without complication (Panel C).

It is well known that AML can be accompanied by embolic events, skin lesions and hyperviscosity. These complications,

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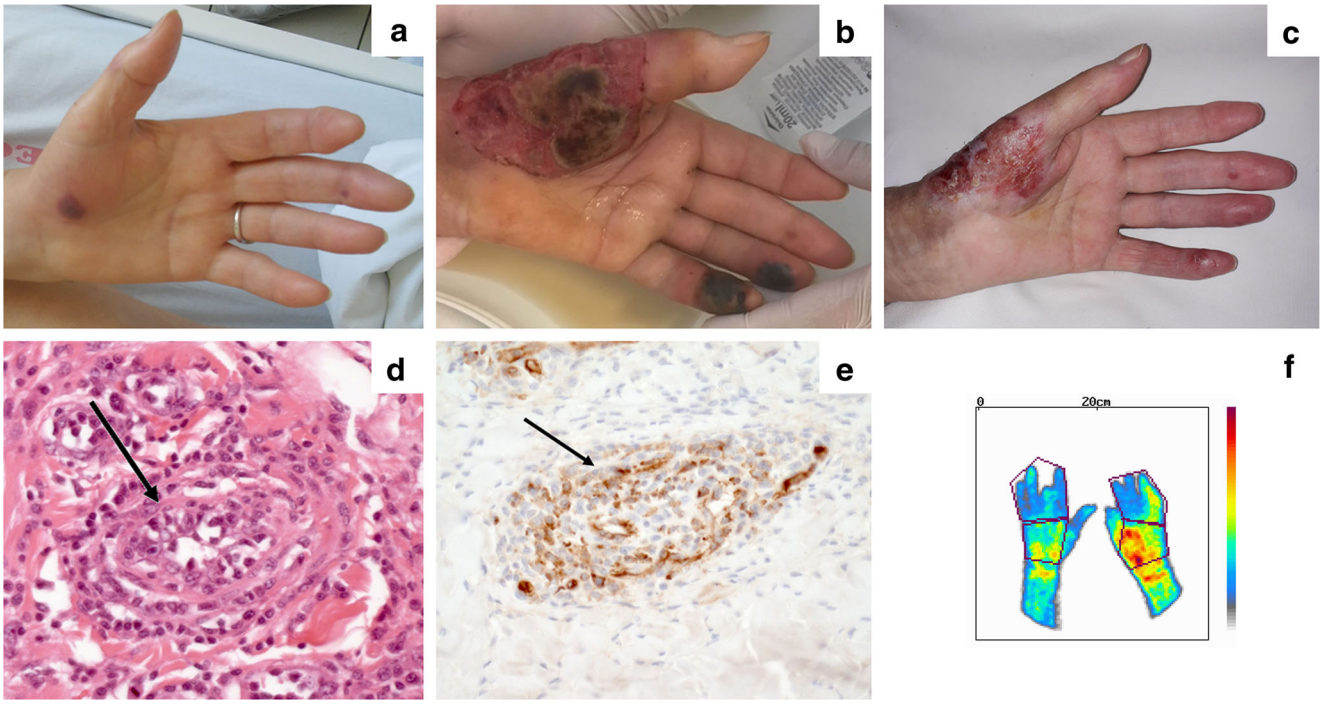

Image 1 Hand lesion of our patient at initial presentation (Panel A), after surgical necrectomy (Panel B) and after 2 months of healing post procedure (Panel C). Histopathological evaluation showed intravascular occlusion and perivascular infiltration by leukemic blast cells (Panel D: hematoxylin and eosin at 400×; Panel E: CD34 at 400×). Tc-99 m hand perfusion scintigraphy presented dysfunction of the microcirculation with impaired perfusion of both hands (Panel F)

however, are most frequently results of thromboembolisation, extramedullary disease manifestation and hyperleukocytosis, respectively [2–4]. In our case we identified a different etiology behind skin lesions of an AML patient: blast cell aggregation led to microvascular thrombosis of the palmar arteriovenous system. It is notable that white blood cell count was within normal range at the initial presentation of skin lesions. Increased viscosity in the palmar microcirculation, direct blast cell invasion into the perivascular space and preferential oxygen utilization by blast cells with resultant hypoxia might also be contributed to the severity of symptoms. Also, treatment with azacitidine proposes median time to best response in over a hundred days after initiation of therapy in previously untreated AML patients [5]. Until then, or in cases of treatment failure, cytoreduction can prevent rare, but potentially organ-threatening or fatal complications.

Considering the absence of clear guidelines and the experience gained with this unique case, we suggest further attempts at cytoreduction in patients receiving azacitidine treatment – even in the absence of hyperleukocytosis.

Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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