letter to the editor
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VASCULITIS AND ALL-TRANS RETINOIC ACID

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Sir,

in their report on all-trans retinoic acid (ATRA) and pseudotumor cerebri in a young adult with acute promyelocytic leukemia, Visani and coll.[1] described a neurologic complication of ATRA administration. Other principal adverse effects of ATRA therapy have also been reported.[2] We wish to describe an unusual skin vasculitis during ATRA therapy.

All-trans retinoic acid induces complete clinical remission in a high percentage of patients with acute promyelocytic leukemia through differentiation of malignant cells into phenotypically mature myeloid cells. Several reports of retinoid (but not ATRA) vasculitis have appeared in the literature, but the mechanism of the immune effects is not clear.[3] The erythema nodosum-like syndrome in these cases may have been a manifestation of leukocytoclastic disease.[4] Only one report[5] has described a vasculitic-like lesion with ATRA, which was interpreted as being correlated with the extent of leukocytosis and not as a hypersensitivity reaction.

We report a case of leukocytoclastic vasculitis with ATRA without hyperleukocytosis that, we think, may have another explanation. A 34-year-old woman presented with pancytopenia. Bone marrow aspirate showed 80% abnormal promyelocytes and cytogenetics revealed the typical translocation between the long arms of chromosomes 15 and 17.[6] No significant coagulation abnormalities were present. Induction treatment with ATRA (45 mg/m^2) and idarubicin (12 mg/m^2 for 4 days) was started.

On day 23, fever and symmetrical painful erythema nodosum-like lesions appeared on the arms and legs. A skin lesion biopsy specimen taken from the patient's right arm showed leukocytoclastic vasculitis. We suspected that this rash was a drug reaction, and ATRA was the only obvious cause. The following tests were normal: urinalysis, serum electrolytes, serum creatinine, serum protein, complement, and liver function tests. Circulating immune complexes and antineutrophil cytoplasmic antibodies (ANCA) were negative. Prednisone (20 mg/day) was given for 3 days to control the symptoms. The papular rash quickly improved and the prednisone was interrupted. ATRA was then continued and no skin lesions reappeared.

In our case, unlike that of Dr. Toh's, leukocytosis was not present even though the bone marrow was recovering. Therefore it is difficult to explain the skin lesion as leukocytosis involvement. Furthermore, skin biopsy showed more of a perivascular eosinophilic infiltrate and only a few neutrophilic leukocytes. On the other hand, due to the fast resolution of these skin lesions after short-term steroid therapy and their non-reappearance even though the patient continued taking ATRA without steroids, we are inclined to exclude an immunological cause. It is difficult to explain this situation.

We would suggest a functional defect secondary to ATRA therapy rather than a leukocytosis-related cause. In fact, leukocyte adherence to capillary endothelial cells and extracellular matrix is mediated by integrins, and genes that encode integrin were recently found to be up-regulated[7] by retinoic acid. Therefore ATRA could increase integrin expression in the maturating cell, which would enhance cell adherence to capillary endothelium.[8] As in Dr. Toh's experience, the course of the lesions was benign in our case. The lesions quickly disappeared with steroid therapy, which was also useful for the pain, and continued treatment with ATRA did not lead to a worsening of the lesions.

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