Cleaning up "Auer" Act in The Aftermath of Acute Promyelocytic Leukemia Treatment

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To the Editor:

Differentiation syndrome (DS) is a serious complication of all-trans retinoic acid (ATRA) or arsenic trioxide (ATO) treated acute promyelocytic leukemia (APL). Its clinical manifestations relate mainly to lung and kidney injury and include respiratory distress, renal failure and third spacing of fluid. The prevailing suggested etiology of DS cites excessive inflammatory response and chemokine overproduction.[1] We herein raise the possibility of direct vascular injury by Auer rods (Figure 1 A) as a potential contributing etiology. We include morphologic images and literature facts that support raising this possibility.

Figures B, C and D are of macrophages from day 29, day 43 and day 57 bone marrows from patients with treated APL. These images exemplify cells often encountered in marrow of ATRA or ATO treated APL patients. They demonstrate that despite macrophages' ability to enzymatically dissolve many materials, Auer rods appear resistant to digestion; rather than dissolving, they persist and stack in piles within macrophages and/or circulate.

Additional observations and facts, when taken in context, may suggest a role of Auer rods in inflicting mechanical injury to vessels and causing DS:

1. One study showed that patients with the M3 variant of APL seem protected from development of DS[2], though the etiology was unclear. Of note, promyelocytes in the microgranular variant of APL show heavy cytoplasmic primary granules, but generally no Auer rods.

2. Most signs and symptoms of DS are related to lung and kidney injuries. Common to these two organs is that circulating blood has to navigate narrow capillaries with delicate vascular endothelial cells. Extrapolating from what we know about the etiology of sickle cell anemia complications, rigid cells (and those with sizable rigid inclusions like Auer rods) are expected to experience additional difficulties and inflict injury.

3. Biochemical studies show Auer rods as densely compacted, azurophilic granules; light and electron microscopic images show them as needle shaped objects with sharp pointed tips.[3]

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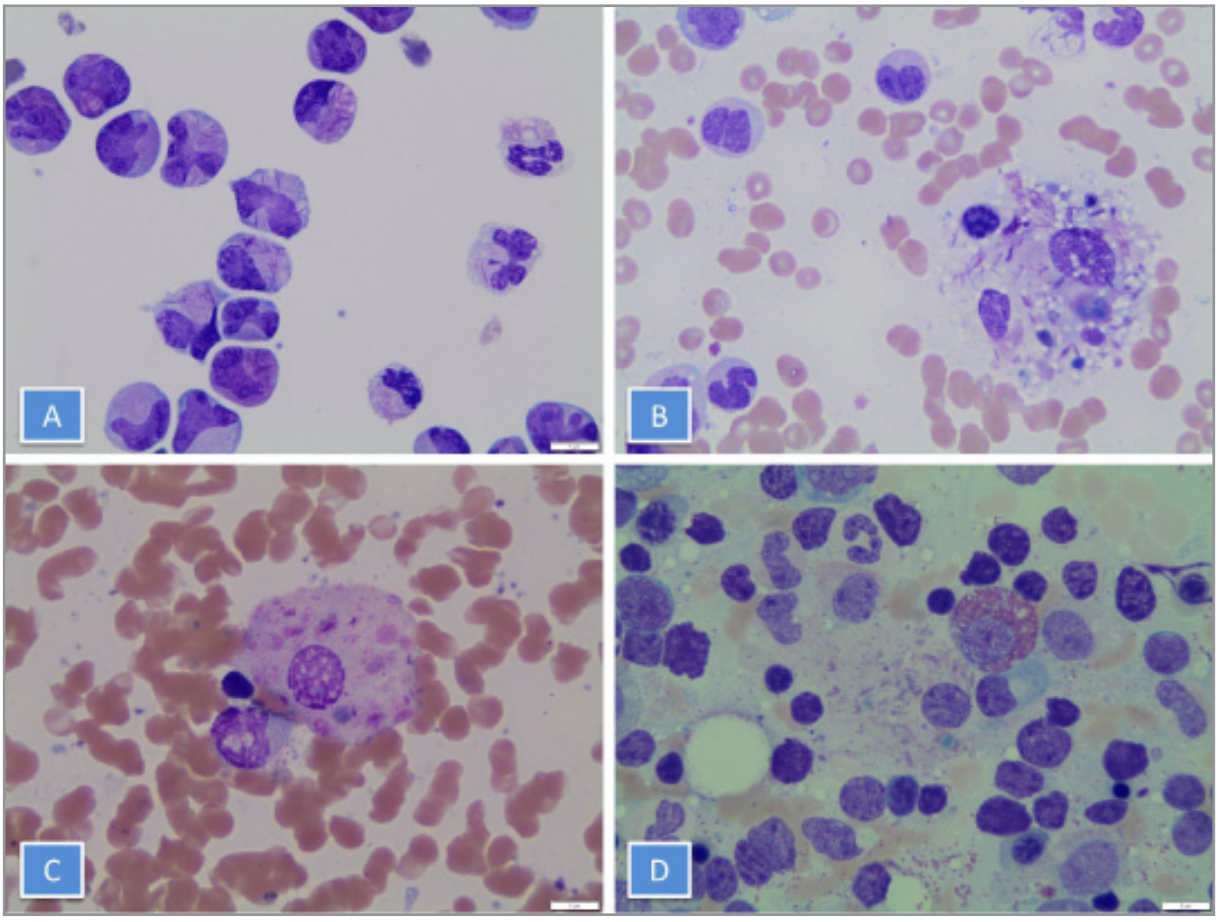

Figure 1. Bone marrow aspirate from a case of APL showing myeloid cells ranging from blasts to band neutrophils showing Auer rods (A). Examples of macrophages with insoluble Auer rods from bone marrow aspirates at day +29, day +43 and day +57 of ATRA treated case of APL (B, C and D).

4. While a "cytokine storm" hypothesis has been postulated as an etiology for DS, this hypothesis does not explain the difference in the incidence of DS between classic APL and the microgranular variant.

5. Furthermore, DS is encountered in treatments that promote differentiation of promyelocytes (helping them mature and enter circulation) rather than treatments that destroy abnormal precursors within the marrow (as expected with chemotherapy). While macrophages may be able to contain dead Auer rod-laden cells in the marrow, leukemic cells maturing and entering circulation retain their Auer rods until they die (and subsequently can get stuck in renal and pulmonary circulations).

Considering the above observations and facts, the following hypothesis deserves further investigation: differentiation syndrome is, at least in part, the result of direct mechanical injury to blood vessels by Auer rods (whether free in circulation or in rigid cells). Testing this hypothesis may be feasible by incorporating the following steps into future clinical trials:

1. Morphologic review to separate cases into classic versus microgranular APL by blinded central review. Results can then be correlated with clinical data (e.g., occurrence of DS).

2. If the protective nature of the microgranular variant is further supported, additional effort should be directed to further study the physical characteristics of Auer rods and find treatments that help

dissolve or filter them from circulation. While corticosteroids can be helpful in controlling/reducing the inflammatory damage in DS, finding a way to dissolve or filter Auer rods from blood may be a way to alleviate this direct injury or prevent it before it starts.

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