To the Editor:

I read with interest the detailed report of Fradera and colleagues that discussed the diagnostic confusion caused by the presence of variably sized azurophilic granules in the cytoplasm of blasts of acute lymphoblastic leukemia (ALL) and described the cytochemical and ultrastructural characteristics of these inclusions. Contrary to the authors’ impression, the occurrence of such granules in ALL is neither uncommon nor unreported. Moreover, several ultrastructurally different organelles can produce inclusions mimicking the azurophilic granules of early myeloid cells at the light microscopic level, and different granules have different cytochemical properties. Anomalous azurophilic granules occurring in blasts and immature cells of lymphoid leukemias can be roughly divided as follows:

- Crystalline: Elongated crystals that can either represent immunoprotein, usually in an envelope of rough endoplasmic reticulum, or nonimmunoglobulin structures with a regular periodicity (often 55 Å), have been reported in chronic lymphocytic leukemia and prolymphocytic leukemia. The inclusions containing ribosomal material are paranuclear, whereas other crystalline inclusions contain acid hydrolases and phosphatases suggesting lysosomal origin. Crystals rich in immunoglobulin often fail to react with Romanowsky stains, producing a clear, rectangular to rhomboidal space in the cytoplasm of the blast or immature lymphoid cell.

- Ribosomal Variants: Malignant lymphoid cells of both chronic and acute lymphocytic leukemias have been reported to contain variably sized azurophilic inclusions that ultrastructurally resemble the lamellar–ribosomal complex of the hairy cell. Anday further reports that granules resembling the lamellar–ribosomal complex possess pyro-nuclease abolished by ribonuclease pretreatment.

- Lysosomal/mitochondrial: Several authors describe azurophilic granules in blasts of lymphoid origin that have been proven by electron microscopy (EM) to originate from lysosomes, mitochondria, or combinations of both organelles. The cytochemical reactions of such granules vary, but most often they are similar to those seen in the cells of the patient of Fradera and colleagues, containing nonspecific esterase and butyrate esterase—usually fluoride resistant—acid phosphatase, and glucuronidase. Many also react to period acid-Schiff (PAS). Rarely, granules of this sort contain lipid and react to Sudan Black B, creating major diagnostic confusion. They do not react with granulocytic specific lysosomal stains such as myeloperoxidase and ASD chloroacetate esterase.

The appearance of such anomalous azurophilic granules in ALL blasts is not unusual, as they were found in ~10% of the new ALL patients studied at St Jude's. Hematologists and pathologists should not diagnose French-American-British (FAB) M1 acute leukemia on the morphological appearance alone, especially in a clinical context more suggestive of ALL. Cytochemical confirmation of the granulocytic origin of the leukemic cells is essential. Given the occasional report of sudanophilic granules in ALL blasts, the stains used should be granulocyte enzyme-specific, such as myeloperoxidase or ASD chloroacetate esterase. Only such testing can avoid the diagnostic problem so well illustrated by Fradera and colleagues.

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REFERENCES


To the Editor:

We read with interest the comments by Dr Richard Savage and would like to clarify one point and perhaps raise others.

When we decided to study and publish our case with the abnormal granules we were convinced, and still are, that we were reporting a most unusual finding. Unfortunately, Dr Savage missed the point of our report. We did not report a case of ALL with azurophilic granulation. Indeed, we were most impressed by the fact that the granules were actually not azurophilic. This was clearly described in the light microscopy section of our report (p 407) and can be observed in the color photomicrographs accompanying the article. The granules were described as dark purple, and we believe that the data as presented illustrated the fact that they appeared more like...
Granulation in all blasts [letter]

RA Savage