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Leukemic Nodules in the Eye in Immature-Cellular Infantile Leukoses

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Summary. Two boys, aged $5^1/_4$ and $10^1/_4$, respectively, with acute immature-cell leukosis, died of massive cerebral haemorrhage. Their eyes showed extensive leukaemic involvement of the retina with development of numerous miliary leukaemic nodules; the vitreous of case 2 was also involved. The lesions were considered to have developed because of high circulating white cell counts, a tendancy of blast cells to produce nodules, an oxygen poor avascular matrix in which to grow, and a physical environment which permitted growth without haemorrhage or distortion due to tissue pressures etc. Using histological methods, an attempt is made to trace the pattern of formation of the nodule, from an initial growing focus through "colonial" form resembling a bacterial colony to lysis. Necrotic blast cells are apparently a metabolic source for viable tumour cells. Their localization in the eye makes access by cytotoxic drugs difficult; thus they should be considered as blast cell pools.

Key words: Leukemia – Infantile leukemia – Leukemic nodule – Eye – Blast infiltrate.

Introduction

We recently reported fatal massive cerebral hemorrhage in three children as the first manifestation of infantile immature-cellular leukoses (Schmid, Mutz et al.). Two boys, aged $5^3/_{12}$ (case 1) and $10^3/_{12}$ (case 2) years, with 899,000 and 361,000 undifferentiated blasts, respectively (lymphoblastic or myelomonocytic cell type), showed pronounced and very unusual histological changes, particularly in the optic fundus.

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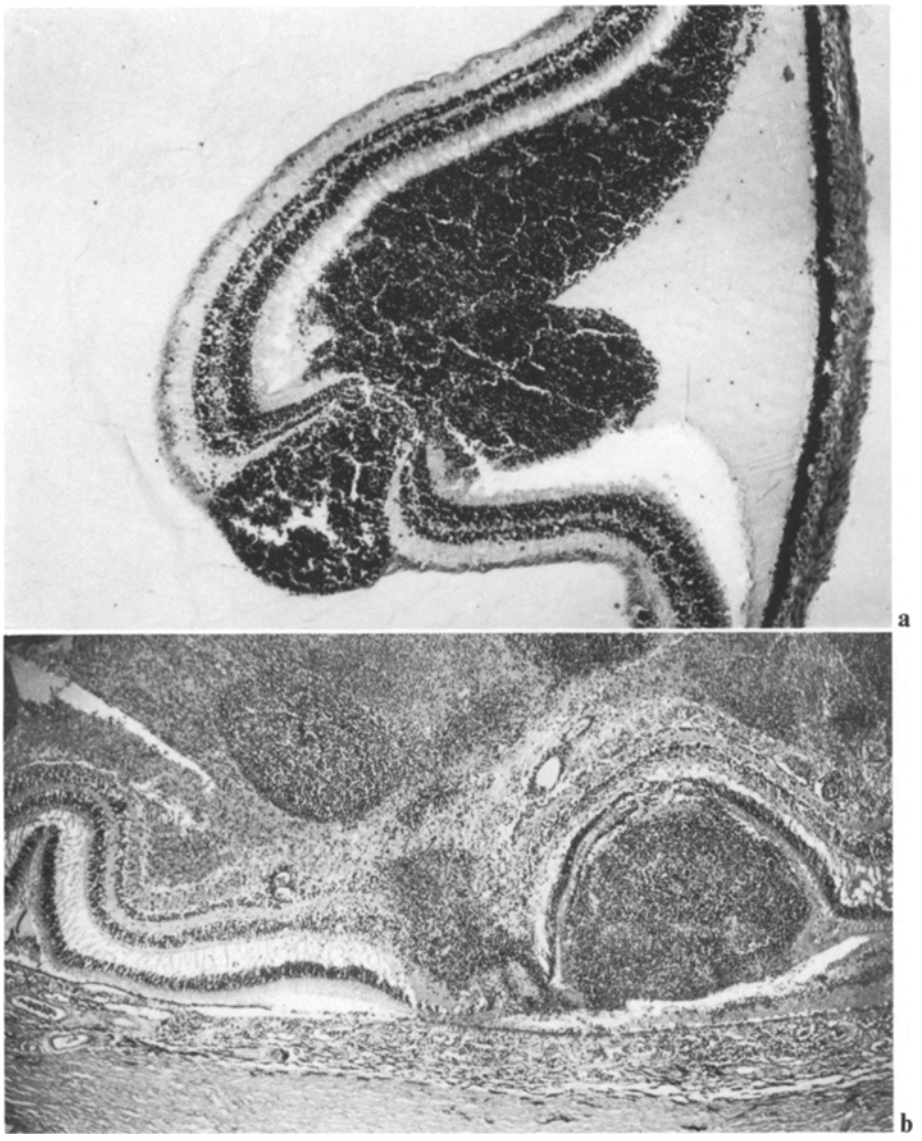

Fig. 1. a Case 1, right globe. Gross, bulging retinal retinal detachment, caused by blasts, both infiltrates developed independently. Perforation of the vitreous body hindered by the intact membrana limit. int. Edema in blastfree ablation area. Paraffin HE, ×30. **b** Case 2 Irregular, locally wrinkled retinal detachment due to leukemic infiltrates (right) and edema (left). Retinal destruction (middle), rupture into the vitreous body with severe, partially nodular blast involvement. Severe edema of Henle's layer with fiber tears (left). Paraffin HE, ×10

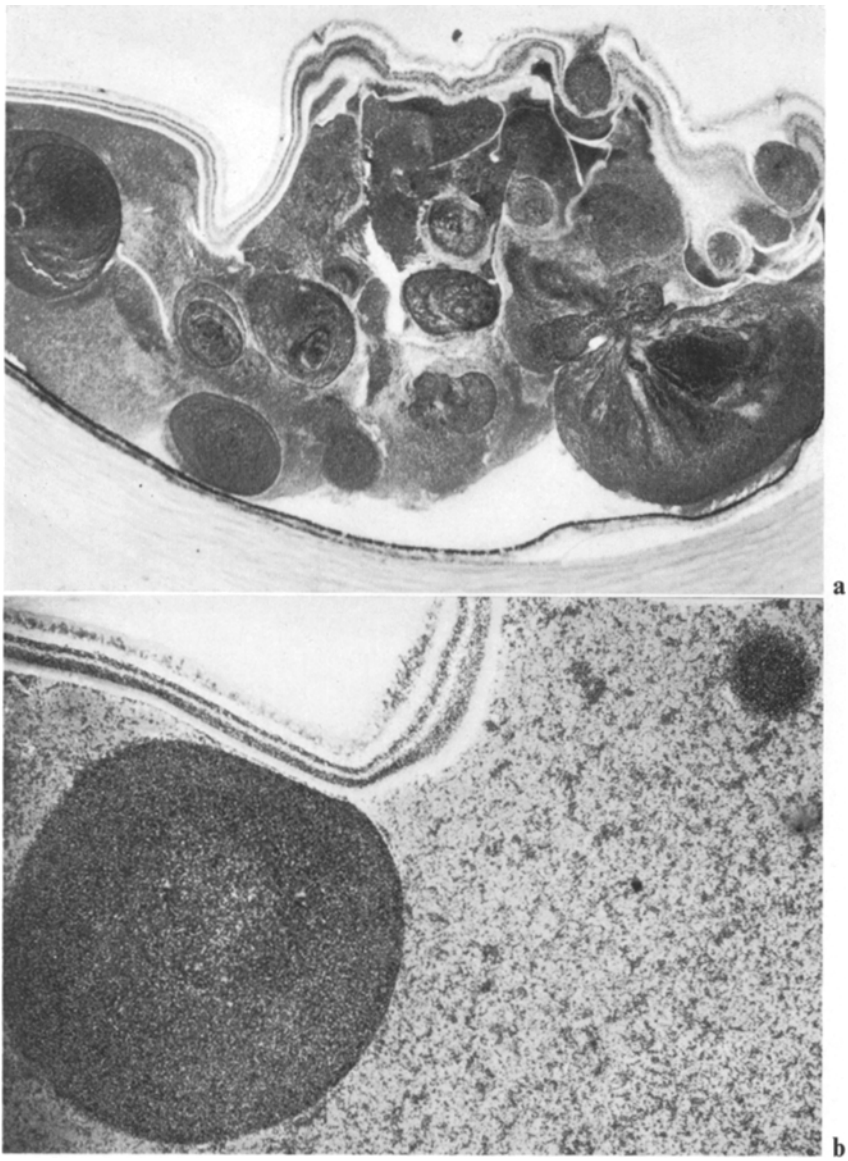

Fig. 2. a Case 2, right globe. Retinal detachment with numerous miliary leukemic nodules in various stages of development, frequently distinct layering, occasional confluence of nodules. Nodules in bloody matrix. Similarity to bacterial culture. Paraffin HE, ×12. **b** Case 1. Ill defined proliferation nidus (upper right) and young, homogeneus leukemic nodule (left) in loose matrix containing erythrocytes and blasts. Paraffin HE, ×25

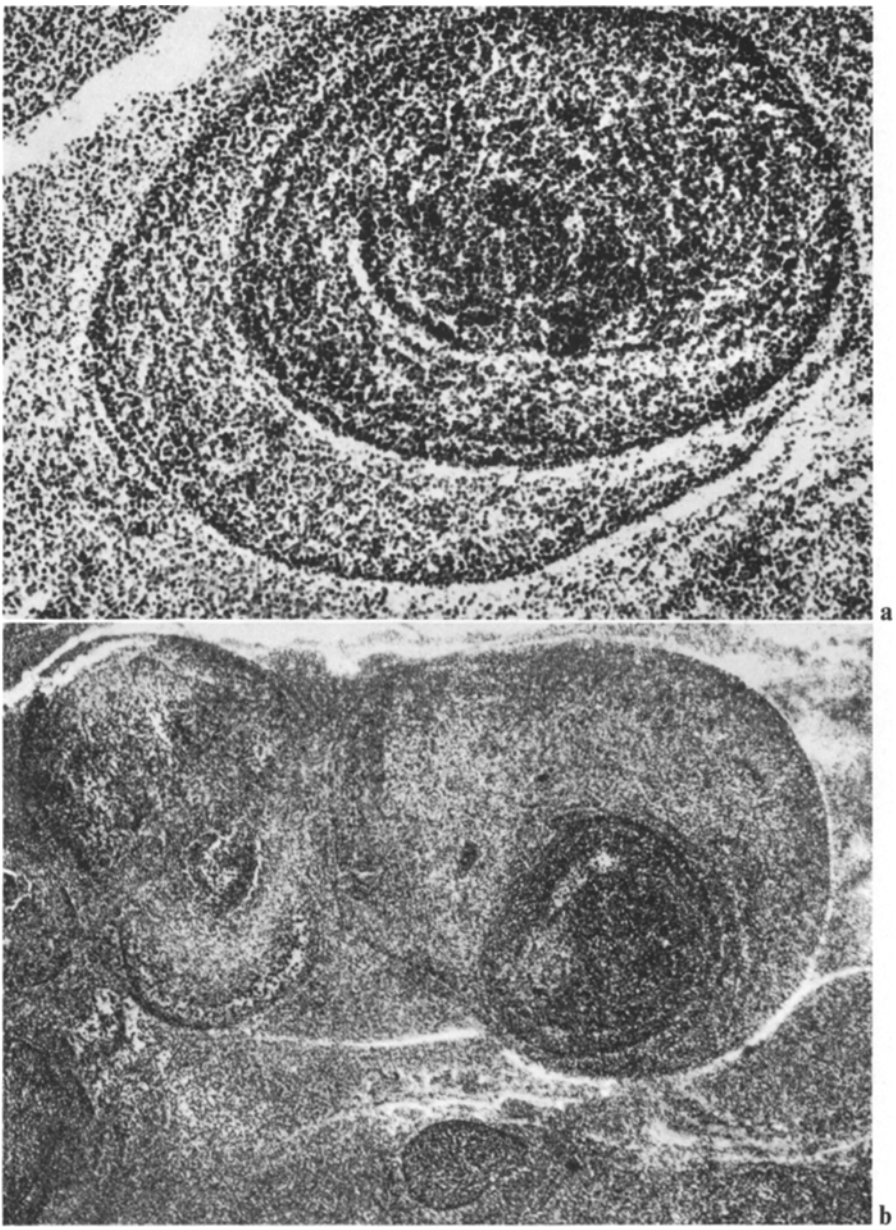

Fig. 3. **a** Case 2. Oval leukemic nodule with broad, excentric growth ring. Paraffin HE, ×75. **b** Case 1. Beginning of confluence of two leukemic nodules. Paraffin HE, ×16

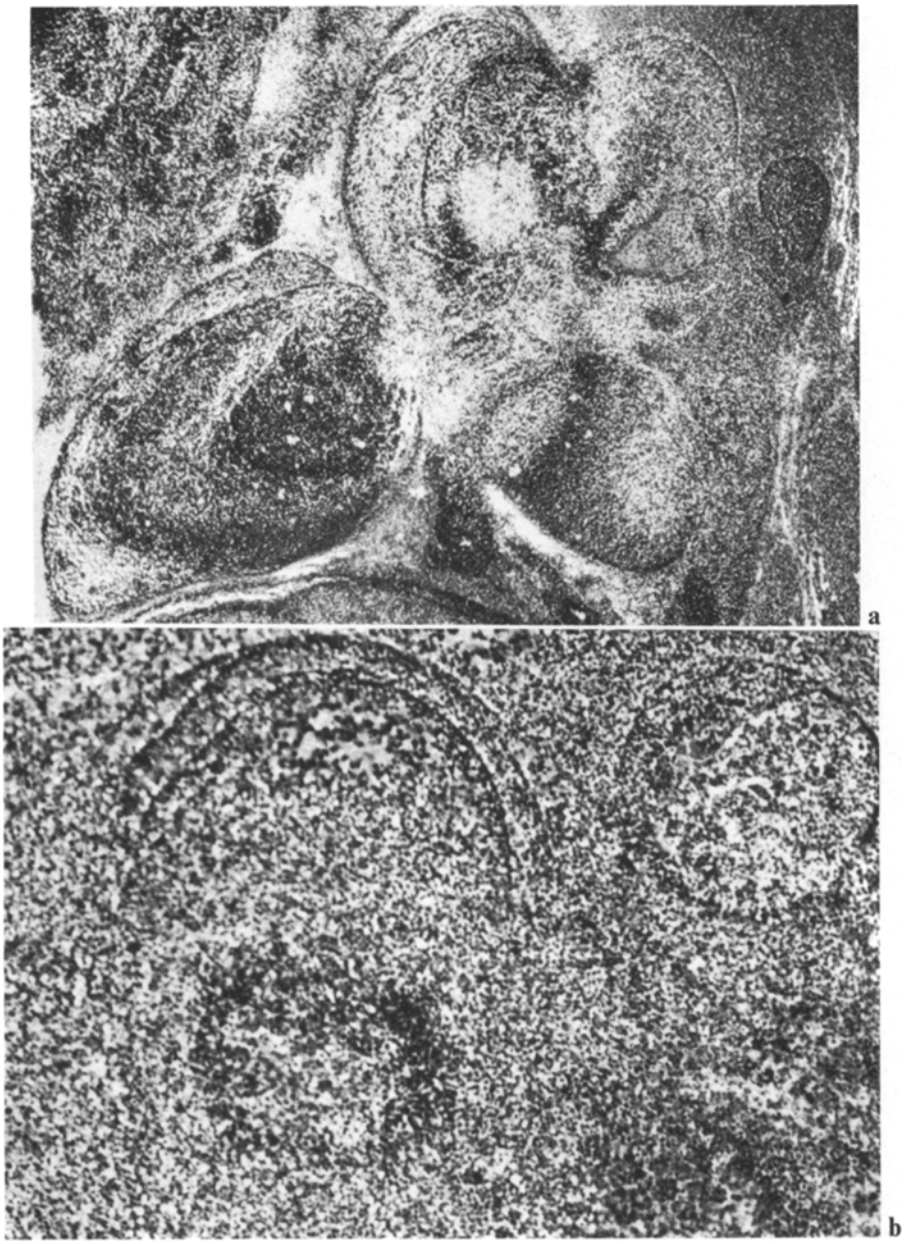

Fig. 4a and b. Case 1. **a** Cloverleaf growth figure, resulting from nodule confluence, with local lysis. Paraffin HE, ×13. **b** Abortive nodule formation in diffuse blast infiltrate. Paraffin HE, ×40

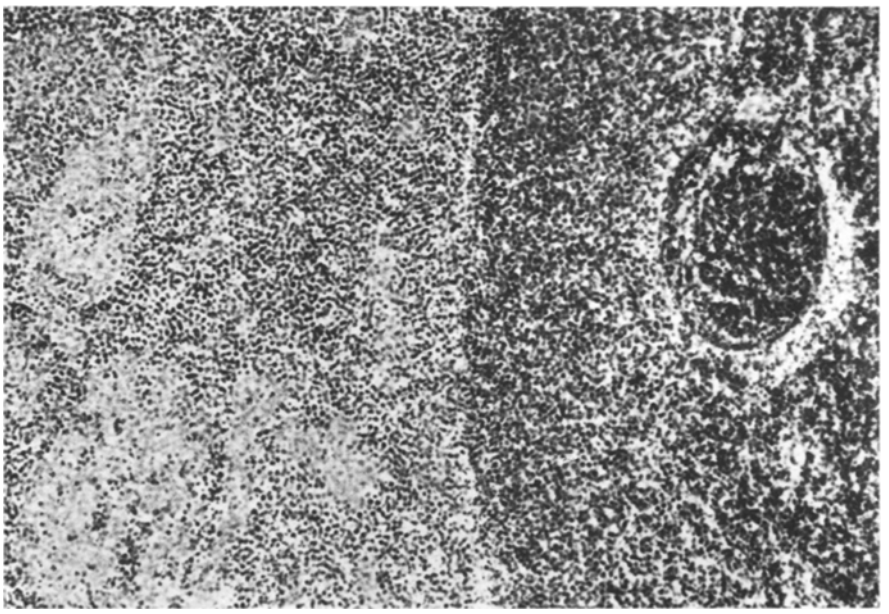

Fig. 5. Case 2. Large, quite sharp defined leukemic nodule with small daughter nodule (right). Motheaten necroses in neighboring diffuse blast group. Paraffin HE, ×40

Clinical and Microscopic Findings

Ophthalmologically, the slightly milky and clouded retina showed large intraretinal streaky hemorrhages, and sizable preretinal hemorrhage. The veins were strikingly wide. Irregular, highly vesicular smooth retinal detachments were found in the periphery of the retina. These were separated by irregular strictures, and were circular in case 1. The hemorrhages bulged toward the vitreous body and were sharply defined, without definite rupture into the vitreous body. They increased in size and number within a few hours.

Histological Examination of the globes shows the leukemic infiltrates to be concentrated in the posterior chamber of the eye (Fig. 1a and b, 2a). They occur multicentrically, mainly in the retina, leading to intraretinal layering and vesicular detachment (Fig. 1a). The hollow space formed by the detachment is filled with serous fluid. Two barely separated intraretinal blast infiltrates (Fig. 1a) are found in a circumscribed area. The inner, smaller infiltrate presses both plexiform and granular layers into larger infiltrate while bulging, mushroom-like, toward the vitreous body. A rupture into the vitreous body is prevented by the membrana limitans interna.

In other areas blast infiltrates or edema cause retinal detachments which may be dome-like, flat or, in places, wrinkled (Fig. 1b). The texture of Henle's layer loosens, with fiber dissociation (Fig. 1b). The choriocapillaris is variably speckled with blasts. In the veins of the choriocapillaris and retina, leukostasis with pronounced blast cell necrosis may occasionally be seen. Interstitial accumulations of blasts are small. In case 2 due to complete destruction of the retina, there is extensive rupture into the vitreous body, with blast cell proliferation and hemorrhage (Fig. 2b). The sclera contains a few venules containing many blast cells but no interstitial infiltrates or hemorrhages. In serial section the optic nerves are sparsely infiltrated with blasts mainly extravasally. Particularly noticeable is the development of numerous, mostly miliary to 2-mm diam. leukemic nodules (Fig. 2a) in the area of the retinal detachment. The nodules vary in structure. There are roundish nodules with diffuse blast cell arrangement (Fig. 2b), larger nodules are sharply defined (Fig. 2b, left); small nodules (Fig. 2b, upper right) are ill-defined against the surrounding "matrix". Numerous nodules show distinct layering (Fig. 2a, 3a, b) and are oval. The accumulated

layers may be wide (Fig. 3a) or narrow and are sharply delineated from each other and their surrounding. Their thickness can vary considerably within a nodule (Fig. 3a, b). Sometimes the nodules deform each other (Fig. 3b) and partially coalesce occasionally in cloverleaf-style (Fig. 4a). Occasionally the development of nodules and layering is abortive resulting in diffuse groups of blasts (Fig. 4b); in other places a denser blast cell node, containing a small daughter node, abutts on loosely strewn diffuse cellular infiltrate with cellular necrosis and a motheaten appearance (Fig. 5). The "matrix" is either serous, or consists of groups of cells variably containing blasts or erythrocytes, but often free of the latter (Fig. 4b, 5). There are no blood vessels in the matrix.

Discussion

Blast cell colonization proceeds from both the choriocapillaris and the retinal end vessel system. The blasts extravasated from the choriocapillaris must first overcome the resistance of the pigment epithelium and its basal membrane and thus can only infiltrate or grow relatively slowly and in limited numbers. In the retinal supply area however there are apparently far fewer texture-dependent hindrances to expansion. The stratigraphic localization of the retinal detachment is typical (in the layer of rods and cones, which is particularly susceptible to damage of many kinds). Regarding the mechanism of retinal detachment, we assume in both cases that initially the leukemic retinal infiltrate developed, and led, after growth beyond a certain critical size, to hypoxia and inadequate nutrition with subsequent lysis of the rods and cones. In addition, severe edema caused substantial tearing of the fibers in Henle's layer (Fig. 1b). The retinal detachment, or retinal dissection, was considerably enhanced by thrombopenic hemorrhage.

The question of the role of the hemorrhage within the framework of the retinal detachment is difficult to asses since, not only erythrocytes but also blasts were "bled". The very pronounced nodular blast infiltration in the area of retinal detachment and subsequent perforation into the vitreum (case 2), is probably due to the lack of vascular or tissue impeding factors acting on the cell. The blast cell clusters form nodular, lymphoma-like infiltrates, often with unusual lamellar layerings. These nodules develop in a matrix of variable composition, consisting in places of a cell-free, protein-rich edema (Fig. 1a), other areas contain numerous (Fig. 2a) erythrocytes probably a result of blood-oozing. Elsewhere the matrix contains loose (Fig. 2b), or dense (Fig. 4b) groups of blasts with a high rate of necrosis (Fig. 5). The initial focus consists of a small, globular blast collection (Fig. 2b, upper left), poorly-defined from its surroundings. The blasts proliferate in a manner resembling a bacterial colony (moist chamber), usually forming oval excentric growth rings (Fig. 2a, 3a) with wide or narrow layers. They are clearly distinguishable from the surroundings.

The formation of nodules appears to be fundamental to blast cells and independent of the type of leukosis developing both in lymphoblastic (case 1) and myelomonocyctic (case 2) leukoses. Since the node matrix is avascular, the nodules probably develop in an O_2-poor environment. Abundant necrobiotic and necrotic blasts are often found in the matrix and in the nodule. We believe that growing leukaemic cells are nourished, in part, from the products of cell degradation, including the blasts (the latter both inside and outside the matrix),

in a form of reutilization. As in bacterial cultures, conclusions as to the cell type involved may not be drawn from the form of the growth. We would point out that cytostatic drugs reach leukemic nodules in this localization poorly, and in low concentration, enabling the nodules to develop into particularly dangerous blast cell pools. Although the relevant textbooks of ophthalmologic histopathology emphasize the relatively frequent involvment of the eyes, especially in acute pediatric leukoses (Kreibig, 1961; Reese, 1966; Hogan and Zimmermann, 1968; Yanoff and Fine, 1975), we found no mention of leukemic nodules. Only Hogan and Zimmermann mention lymphocytic tumour formation in the area of retinal hemorrhage in lymphatic leukemias. In the extensive survey by Allen and Straatsma (1961) formation of macroscopically visible nodules one case is mentioned with no further details. Kuwabara and Aiello (1964), however, report a 60-year-old man with chronic myeloid leukemia with numerous miliary leukemic nodules in the retina, but without the unique lamellar structure and confluence of the nodules which we observed.

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