Jordans' Anomaly in White Blood Cells

Report of Case

By L. ROZENZAJN, A. KLAJMAN, D. YAFFE AND P. EFRATI

In 1953 Jordans' described fat-containing vacuoles in the leukocytes of peripheral blood in 2 brothers, both of whom had progressive muscular dystrophy.

This case report deals with a family in whom 2 sisters were affected with ichthyosis; vacuoles were observed persistently in the leukocytes of both sisters. In the bone marrow, vacuoles were found in cells of the myeloid series. Cytochemical examinations were performed to determine the nature of these vacuoles.

FAMILY HISTORY

The 2 affected sisters immigrated to Israel from Iraq. The parents, first cousins, had 13 children. Six of the children were dead; among these were 2 sons and 1 daughter with ichthyosis, but no blood examinations had been performed on them.

The parents of the 2 propositi, their 7 children and grandchildren, as well as the parents’ sisters and their children, were investigated by us (Fig. 1). Ichthyosis and vacuoles in leukocytes were found only in the 2 sisters.

CASE REPORT

N. N. (Fig. 2) a 19-year-old girl, had had ichthyosis from early childhood; otherwise she had always been healthy. The physical examination was negative except for ichthyosis involving all the areas of the body with the exception of the face. The skin was thickened and dry and was covered with greyish-brown scales of variable size. The type of ichthyosis was diagnosed as ichthysiform erythrodermia. There was no enlargement of lymph nodes; the liver and the spleen were not palpable.

Laboratory investigations revealed leukocytes 9.100/cu. mm., the differential count: band forms 1 per cent, mature polymorphonuclears 62 per cent, eosinophils 2 per cent, lymphocytes 29 per cent, monocytes 6 per cent. Blood sedimentation rate (Westergren) 25/50; blood urea 21 mg per cent; glucose 102 mg per cent; oxalacetic transaminase 25 units, oxalpyruvic transaminase 38 units, alkaline phosphatase 4.7 Bodansky units. Kahn test negative; blood proteins 6.9 Gm. per cent, albumin 4.3 Gm. per cent, globulins 2.6 Gm. per cent, electrophoresis of serum proteins normal. Total lipids 516 mg per cent, fatty acids 280 mg per cent, phospholipids 8.1 mg per cent, cholesterol 164 mg per cent. Chromatography for urinary amino acids did not reveal any abnormalities; amino acid nitrogen in urine was 204 mg./24 hours (normal 200-700 mg.). Urinanalysis was normal.
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Fig. 1.—Pedigree of the family. "Plus" = died in childhood; "plus inside circle" = ichthyosis and Jordans-like traits; "plus inside square" = ichthyosis. Blood not examined.

The second sister, I. N., showed no abnormalities on physical examination except for ichthyosis. Laboratory investigations were normal, the only pathologic finding being vacuoles in leukocytes.

MATERIAL AND METHODS

Peripheral blood and bone marrow of the 2 sisters were examined. Light and phase microscopy were used. Fluorescent microscopic studies were done with acridine orange (A. O.), neutral red (N. R.), and rhodamine B (R. B.).

The A. O. dye was prepared as a 10 mg./100 ml., the N. R. and R. B. dyes as 0.1 Gm./100 ml. solutions in Sörensen buffer M/15 to pH 6.3. One drop of peripheral blood or bone marrow aspirate was placed on a clean slide and mixed with a drop of one of the fluorescent dyes. A coverslip was then applied and the edges were sealed with Vaseline.

The other stains used were May-Grünwald-Giemsa, periodic acid Schiff (P. A. S.) reaction with and without ptyaline digestion, Sudan black B, and stains for alkaline phosphatase, acid phosphatase, and peroxidase staining for general diagnosis.

Sudan III staining was carried out as follows: 2 to 3 drops of Sudan III, 0.3 Gm. per cent in 70 per cent alcoholic solution, were spread on the smear for 2 to 3 minutes; subsequently 2 to 3 drops of 1 per cent solution of brilliant cresyl blue were added for 3 to 4 minutes and afterwards the excess of dye was removed; a cover glass was placed on top and the smear was examined.
RESULTS

Staining with May-Grünewald-Giemsa Method. Peripheral blood: In thrombocytes and erythrocytes of both sisters no abnormalities were detected. In all their neutrophils 3 to 10 round vacuoles were seen; they varied in size from 2 to 5 μ (Fig. 3); in eosinophils (Fig. 3) and basophils (Fig. 4) vacuoles were observed which were similar, but fewer in number. Vacuoles were found in 80 per cent of monocytes (Fig. 5) and 3 per cent of lymphocytes of one sister (N. N.) and 72 per cent of monocytes and 6 per cent of lymphocytes of the second sister (I. N.).

Bone Marrow Studies. There was normal proliferation of the erythrocytic and megakaryocytic series. No vacuoles were observed in these cells. Vacuoles were seen in promyelocytes (Fig. 6), myelocytes, metamyelocytes and polymorphonuclears, but not in myeloblasts. The distribution of vacuoles in the immature granulocytes is given in Table 1. A few plasma cells contained 1 or 2 large vacuoles (Fig. 7) which were much larger than those usually found.

Phase Microscopy of Fresh Preparations. The vacuoles appeared as round shiny bodies 1 to 4 μ in size. They were observed in myelocytes, granulocytes, monocytes, but rarely in lymphocytes and plasma cells (Figs. 8 and 9).

Acridine Orange Fluorescence. Nuclei emitted a green fluorescence,
cytoplasm a red fluorescence. On the red background the vacuoles appeared as black round bodies without any fluorescence.

Neutral Red Fluorescence. An orange fluorescence stronger in the cytoplasm than in the nuclei was observed. The vacuoles appeared as round bodies emitting a strong pale-green fluorescence. Between cells were scattered globules of different sizes giving light pale-green fluorescence.

Rhodamin B Fluorescence. The cells emitted an orange fluorescence, more intensive in the cytoplasm than in the nuclei. The vacuoles emitted a dark-green mat fluorescence.

Cytochemical Studies. The cytochemical studies gave normal results. The vacuoles did not take up any of the stains except for Sudan III, which stained the vacuoles from pink to red.

DISCUSSION

To the best of our knowledge persistent sudanophilic vacuoles in granulocytes of peripheral blood have been described only by Jordans in 2 sibs
suffering from muscular dystrophy. PAS-positive vacuoles have been described in lymphocytes in lipidoses.\(^7\) Granulocytes, monocytes and mesothelial cells from ascites and pleural effusions often contain sudanophilic vacuoles. We examined 7 additional cases of ichthyosis and 12 cases of muscular dystrophy, but in none did we observe vacuoles in leukocytes.

We did not find any vacuoles in blasts (Fig. 8). The youngest cells that contained vacuoles were promyelocytes (Fig. 6). Interestingly enough, in promyelocytes there was only one vacuole, and as the cells matured the percentage of cells containing more than one vacuole increased (Table 1). We believe therefore that the vacuoles developed in the cells during their maturation in the bone marrow and were not acquired during their sojourn in peripheral blood. Vacuoles were found less frequently in monocytes and lymphocytes, but never in erythrocytes and thrombocytes or their precursors. The cytochemical studies demonstrated that the vacuoles contained lipids; they gave positive staining with Sudan III and N. R. and R. B. fluorescence. We
could not demonstrate any abnormalities in blood lipids and blood chemistry.

Our genealogical studies of the affected family (Fig. 1) revealed that ichthyosis occurred in 3 sisters and 2 brothers whose parents were first cousins. The parents and their immediate ancestors were not affected, and therefore the disease must have been transmitted through a recessive gene. As both brothers and sisters had ichthyosis, sex-linked transmission is excluded. We can conclude that ichthyosis occurred in the above-mentioned family as a recessive-hereditary factor, determined by a single autosomal gene. It is interesting that the only 2 cases with Jordans anomaly were found in the living subjects suffering from ichthyosis. This rare disease has not been found in any of the other living members of this large family, and the possibility that these 2 phenomena exist in the same subject coincidentally is an unlikely one, and other possibilities should be considered.

It may be that the anomaly in leukocytes is the result of a pleiotrophic effect of the gene which determines ichthyosis and that this effect is expressed only
in extreme cases, for which reason it has not been discovered until now. Another possibility is that different alleles or unrelated genes may cause independently ichthyosis-like traits. Our cases may be such a variant, unpublished until now, having a pleiotrophic effect which is characterized by anomalies in leukocytes.

Jordans anomaly was first described in 2 patients with muscular dystrophy. It is possible also that this anomaly is a secondary nonspecific expression to severe metabolic or developmental disturbances, such as ichthyosis or muscular dystrophy.

**SUMMARY**

Persistent vacuoles were seen in the protoplasm of granulocytes, monocytes and occasional lymphocytes of 2 sisters suffering from ichthyosis. In the bone marrow these vacuoles were found in the cytoplasm of promyelocytes, myelocytes, metamyelocytes and rarely in plasma cells. They were not observed in blasts or in red cells and thrombocytes and their precursors.

**Table 1.**—*The Relation Between the Number of Vacuoles and the Immaturity of Granulocytes*

<table>
<thead>
<tr>
<th>Bone Marrow Cells</th>
<th>Patients</th>
<th>Number of Vacuoles/Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Myeloblasts</td>
<td>N. N.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>I. N.</td>
<td>0</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>N. N.</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>I. N.</td>
<td>64</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>N. N.</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>I. N.</td>
<td>46</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>N. N.</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>I. N.</td>
<td>37</td>
</tr>
</tbody>
</table>
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With the help of cytochemical staining technics and fluorescence microscopy studies, it was determined that the vacuoles contained lipids. A similar abnormality of leukocytes was described previously by Jordans in 2 brothers suffering from muscular dystrophy.

Ichthyosis was transmitted in this family in an autosomal recessive way.

ACKNOWLEDGMENTS

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REFERENCES

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