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Dorfman-Chanarin Syndrome in a Turkish Kindred: Conductor Diagnosis Requires Analysis of Multiple Eosinophils

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Dorfman-Chanarin syndrome is a rare, autosomal recessive inherited lipid storage disease with congenital ichthyotic erythroderma due to an acylglycerol recycling defect. Demonstration of lipid vacuoles in neutrophils from peripheral blood smears (Jordans' anomaly) in patients with ichthyotic erythroderma leads to the diagnosis. In spite of frequent liver, muscle, ear, eye and central nervous system involvement, Dorfman-Chanarin syndrome may present clinically as monosymptomatic ichthyosis. Here, we report clinical and laboratory investigations in a consanguineous family from Turkey with 3 affected family members, and demonstrate the lipid vacuoles in epidermal Langerhans' cells for the first time. Langerhans' cell phenotyping suggests that the skin inflammation is due to the gene defect and not to underlying atopic dermatitis. Microscopic examination of eosinophils for lipid vacuoles to identify conductors revealed variable percentages of normal and vacuolized eosinophils in conductors, suggesting the microscopic analysis of at least 10 eosinophils for conductor identification. ***Key words: Jordans' anomaly; congenital ichthyotic erythroderma; neutral lipid storage disease; Langerhans' cell phenotyping; electron microscopy.***

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Dorfman-Chanarin syndrome is a rare, autosomal recessive inherited lipid storage disease (1, 2). Skin manifestations present as moderate to severe forms of congenital ichthyotic erythroderma. Demonstration of lipid vacuoles in neutrophils from peripheral blood smears in patients with ichthyotic erythroderma usually leads to the diagnosis. Possible extracutaneous manifestations include fatty liver, myopathy, cataract and a variety of neurological symptoms (3). Since the suspected diagnosis can easily be confirmed by examination of a peripheral blood smear, dermatologists must be aware of this disease.

A 16-year-old Turkish boy, who was already diagnosed as having Dorfman-Chanarin syndrome some months ago at our department (4), asked if we could also examine other members of his family who lived in France. He arranged a visit of the entire family at our department for clinical examination (Fig. 1). During this visit, 2 additional members of the family were diagnosed as having Dorfman-Chanarin syndrome, 6 of the 7 unaffected family members were diagnosed as conductors by vacuole demonstration in the eosinophils (Table I). Since the best method for conductor identification is still a matter of debate (5), this report focuses on clinical aspects of this family and the appropriate number of eosinophils to be investigated for conductor identification.

Table. I. *Laboratory analysis in a family with Dorfman-Chanarin syndrome (DCS)*

Patient no.	Eecc	Emic	Vac/e	CK	Notes
III/2	3.0	2	5/10	53	Evident conductor
III/5	1.9	0	2/10	28	Evident conductor
III/6	1.4	2	6/10	30	Evident conductor
IV/2	1.4	1	0/10	32	Probably non-conductor
IV/4	2.5	3	4/10	46	Conductor
IV/5	3.0	3	4/10	nd	Conductor
IV/6	1.8	0	10/10	133	DCS, case 1
IV/9	0.8	0	10/10	158	DCS, case 2
IV/10	1.5	1	10/10	249	DCS, case 3
IV/11	2.3	1	2/10	28	Conductor

Eecc: percentage of eosinophils determined by electronic cell counter; Emic: percentage of eosinophils determined by microscopic examination; Vac/e: number of eosinophils containing vacuoles/total number of analysed eosinophils; CK: creatinine kinase; nd: not done.

CASE REPORTS

Case 1

A 16-year-old boy (Fig. 1, patient IV/6) was born with scaly skin lesions of the face and neck, which subsequently affected the entire body. The consanguineous parents were first cousins. Maldescensus testis and hepatomegaly were diagnosed in early childhood. His fathers half-sister (Fig. 1, patient III/1) was said to be born "with the same skin affection" and had died at the age of 8 months for unknown reasons.

The entire body, including the palms, soles and face, showed an orange-red, slightly scaly ichthyotic erythroderma with dirty-brownish ichthyosiform scales. Knees, elbows, the back of the hands and the upper legs were affected by moderate lichenification. An accessory nipple and particularly small, low-set ears were present.

Histological examination of the skin showed regular acanthosis, papillomatosis, hypergranulosis and orthohyperkeratosis. Within the upper dermis, some lymphohistiocytic infiltration was present.

Electron microscopic examination of the skin revealed lipid vacuoles of variable size and osmiophily in keratinocytes from the stratum basale, granulosum and corneum, but not the stratum spinosum (Fig. 2). Furthermore, cytoplasmic lipid vacuoles were present in many dermal cells, such as fibroblasts, pericytes, mast cells (Fig. 3) and epidermal Langerhans' cells (Fig. 4).

Langerhans' cell phenotyping, a recently standardized flow cytometric procedure helpful in the differential diagnosis of inflammatory skin lesions (6), was performed. A marked expression of the thrombospondine receptor CD36 (rFI = 17.9) witnessed the inflammatory micromilieu of the epidermal compartment. Fifty-nine percent of the inflammatory dendritic epidermal cells (IDEC) (7) contributed to the CD1a positive epidermal dendritic cell pool,

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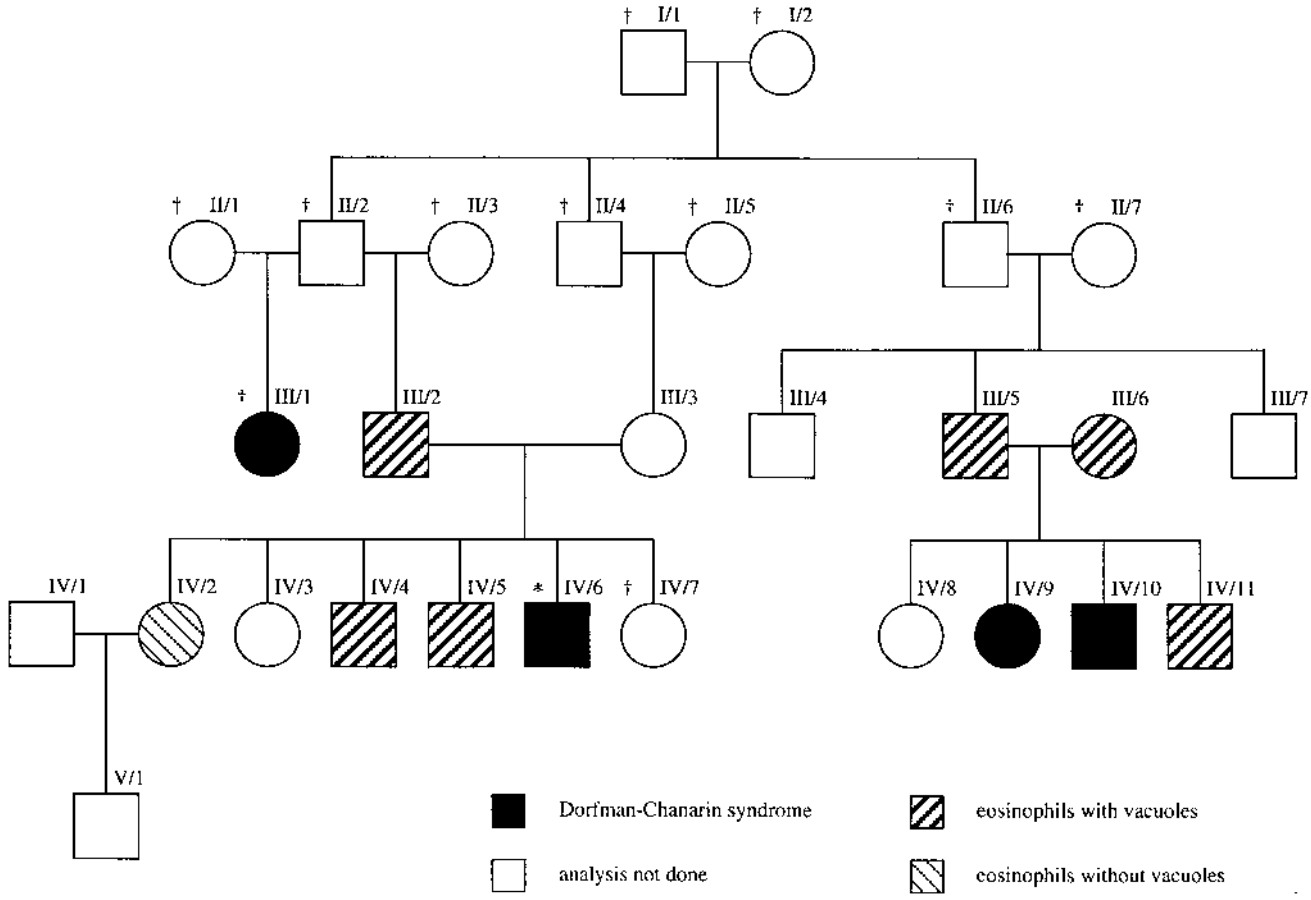

Fig. 1. Pedigree of the family with Dorfman-Chanarin syndrome with results of the leukocyte analysis and patient numbers.

further reflecting the local inflammation induced by the inherited disorder of lipid metabolism. The FcεRI/FcγRII-ratio, known to be elevated in chronic atopic dermatitis lesions, was calculated from the respective rFI values as described. However, the low FceRI/FcgRII-ratio of 0.6 did not suggest an underlying atopic dermatitis (8).

Case 2

A 16-year-old girl (Fig. 1, patient IV/9) of Turkish origin was born without skin abnormalities. At the age of 6 months she developed ichthyotic erythroderma. Her mother was known to be related to her husband some generations earlier, but the exact nature of consanguinity was unknown. The girl was attending a normal high school in France without problems.

A recent audiogram revealed no abnormality. Daily skin care with urea-containing emollients was necessary to maintain an acceptable skin status.

On physical examination, ichthyotic erythroderma with massive lichenification was found to be present on the entire body, including the flexural regions. Her palms showed hyperlinearity and there was a dark-brownish scaling on the back of her hands.

Normal laboratory values included GOT, GPT, gGT, lactate dehydrogenase, bilirubine, creatinine, cholesterine, triglycerides, HDL and LDL fraction. The creatinine kinase was raised to 158 U/l (10–80 U/l) and alkaline phosphatase to 737 U/l (475–617 U/l). Cell counter analysis of leukocytes and thrombocytes gave normal results, but microcytosis and hypochromasia of erythrocytes was detected. Examination of blood smears revealed lipid vacuoles in neutrophils, eosinophils and monocytes.

Case 3

Her brother, a 13-year-old boy (Fig. 1, patient IV/10), was born with ichthyotic erythroderma. According to his parents, he tended to develop blisters from mechanical friction more easily than other children and showed delayed wound healing. He was wearing glasses and was attending a normal high school in France without problems. At a height of 143 cm, he was one of the smallest boys in his class. His skin status had always been worse than his sister's.

On physical examination, an ichthyotic erythrodermic skin was covered with large ichthyosiform, dark-brownish to black scales. The palms showed hyperlinearity. Livedo reticularis and a few blisters were present on his legs. There was abnormal growth of the teeth. Despite daily applications of emollients, the dark ichthyosiform scales were refractory to treatment.

Normal laboratory values included GOT, GPT, gGT, lactate dehydrogenase, bilirubine, creatinine, cholesterine, triglycerides, HDL and LDL fraction. The creatinine kinase was raised to 249 U/l (10–80 U/l) and alkaline phosphatase to 1120 U/l (475–617 U/l). Cell counter analysis of erythrocytes, leukocytes and thrombocytes gave normal results. Examination of blood smears revealed lipid vacuoles in neutrophils, eosinophils and monocytes.

DISCUSSION

In 1974 Dorfman et al. (1) described a new subtype of congenital ichthyosiform erythroderma, which was delineated from other subtypes by lipid vacuoles in peripheral blood granulocytes. These lipid vacuoles were first described by

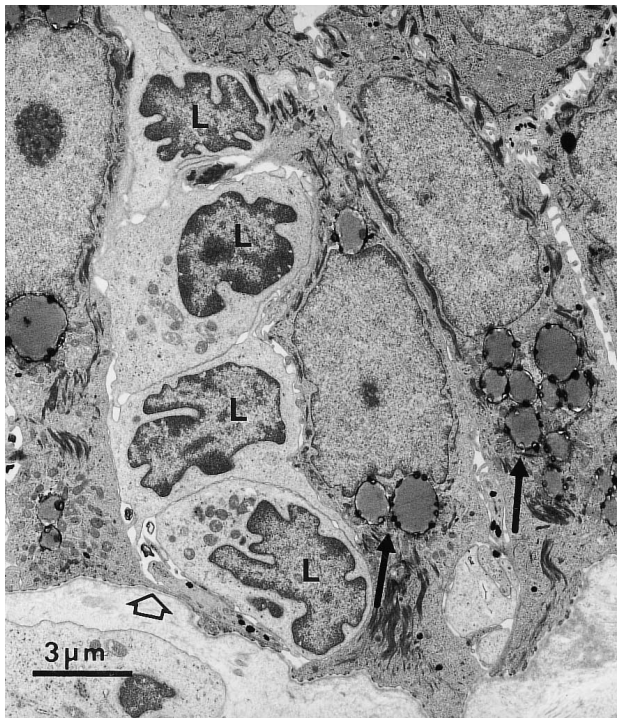

Fig. 2. Electron micrograph of keratinocytes in the basal layer (case 1). Multiple prominent lipid droplets (*long arrows*) within the cytoplasm of the keratinocytes are visible. Several intraepidermal situated lymphocytes without vacuoles are demonstrated (L). Basement membrane (*short arrows*) (× 4,300).

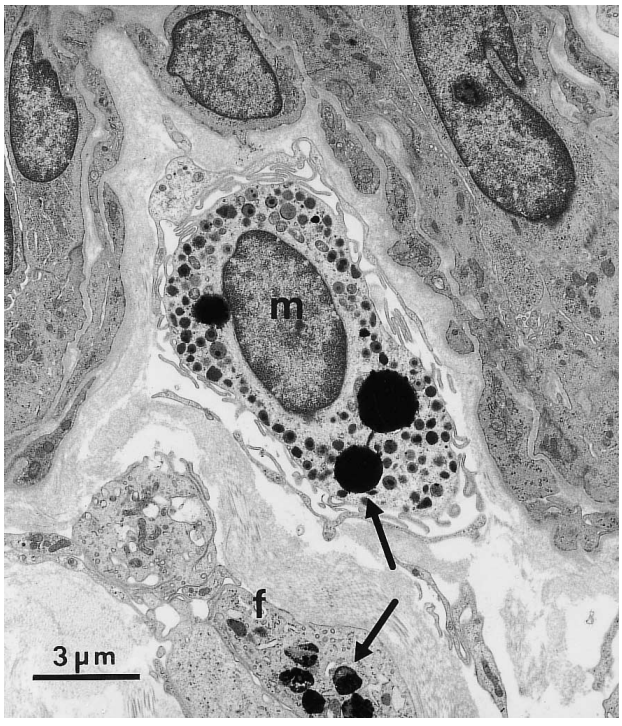

Fig. 3. Electron micrograph of a dermal situated mast cell (m) and a fibroblast (f) with cytoplasmic lipid inclusions (*arrows*) (case 1) (× 4,700).

Jordans in 1953, (9) and are hence often referred to as Jordans' anomaly (10). The independence of this new disease entity was soon confirmed by subsequent case reports from other countries (2, 11). The name "neutral lipid storage disease" was proposed for the new disease from Chanarin et al. (2). Today it is mostly referred to as Dorfman-Chanarin syndrome. Including this report, 32 patients have been described in the literature (Table II).

Dorfman-Chanarin syndrome may be defined as an autosomal recessive, congenital ichthyotic erythroderma with obligate deposition of cytoplasmic neutral lipid vacuoles in various cells of the human body, especially in keratinocytes and granulocytes (9). In addition, lipid inclusions were described until now in monocytes, mast cells, fibroblasts, megakaryocytes, pericytes, muscle cells and Schwann cells but not within lymphocytes, normoblasts, red blood cells and platelets (1, 12–14). These results could be confirmed by our investigations and beyond this we were able to demonstrate lipid droplets in epidermal Langerhans' cells for the first time. Extracutaneous manifestations of Dorfman-Chanarin syndrome may be present, such as hepatosplenomegaly with fatty liver degeneration, but mostly normal aminotransferases. Double-sided cataracts may be present in early childhood or develop later in life. Growth retardation may be present and particularly small, low-set ears are present, at least in the family described here. Despite the commonly raised muscle enzymes, muscle weakness is rarely observed. Neurological manifestations may include ataxia, bilateral neurosensory hearing loss and horizontal nystagmus (3). A defect of acylglycerol recycling from triacylglycerol to phospholipid has recently been identified in fibroblasts from patients with Dorfman-Chanarin syndrome (15), however, no single gene defect for this syndrome has been identified.

The differential diagnosis of Dorfman-Chanarin syndrome includes many, mostly rare, diseases with an ichthyotic

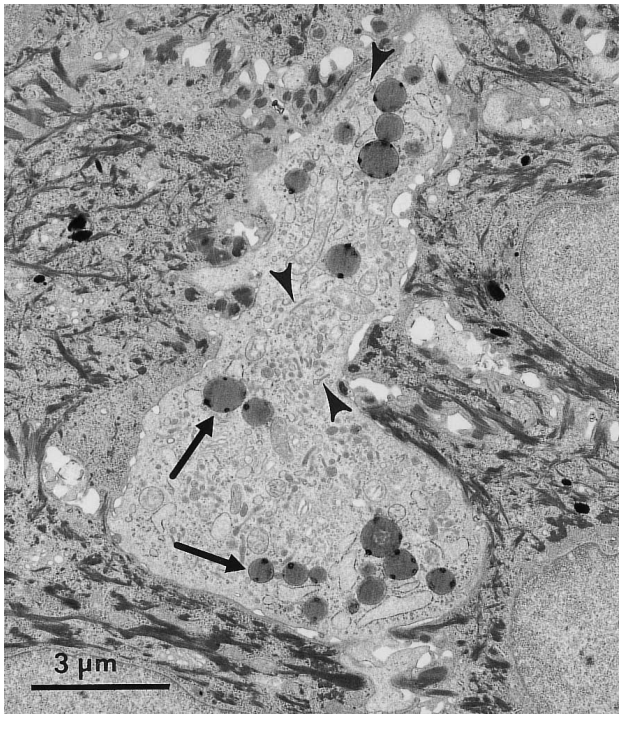

Fig. 4. Electron micrograph of an intraepidermal situated Langerhans' cell (case 1) with typical lipid vacuoles (*arrows*) and Birbeck granules (*arrow heads*) (× 6,000).

Table. II. *Synopsis of clinical features from all published patients with Dorfman-Chanarin syndrome*

No.	Reference	Age	Sex	Consanguinity	Neuromuscular symptoms	Creatinine kinase	Eye symptoms	Liver symptoms	Neuro-sensural deafness	Varia
1	Rozenszajn (10)	35 y	F	Cousin 1°	Yes	Normal	Cataract	?	Yes	Diabetes mellitus
2	"	26 y	F	"	No	?	None	Yes	Yes	
3	"	10 m	F	"	?	?	?	?	?	
4	"	7 d	M	"	?	?	?	?	?	
5	"	6 m	M	"	?	?	None	Yes	?	
6	Dorfman (1)	21 y	M	Cousin 1°	No	?	None	Yes	No	
7	"	16 y	M	?	No	?	None	Yes	No	
8	Chanarin (2)	22 y	F	No	Yes	Pathological	None	Yes	No	Bowel involvement
9	Miranda (11)	41 y	M	No	Yes	?	None	Yes	Yes	Glutene sensitivity
10	Angelini (19)	5 y	F	No	Yes	Pathological	Cataract	Yes	No	Bowel involvement
11	Williams (17)	46 y	M	Cousin 1°	Yes	Pathological	Cataract	?	Yes	Aortic insufficiency
12	"	13 y	M	Yes	Yes	Pathological	Cataract	?	Yes	
13	"	12 y	M	Yes	Yes	Pathological	Cataract	?	Yes	Small stature
14	"	5 y	F	Yes	Yes	Pathological	Cataract	Yes	Yes	
15	Srebrnik (12)	24 y	F	Cousin 1°	No	Normal	?	Yes	Yes	Intelligence reduction
16	"		F	Cousin 1°	No	Normal	Cataract	Yes	?	Intelligence reduction
17	Muscumeci (18)	2 y	M	No	No	Pathological	None	No	No	
18	Wolf (5)	3 y	M	Cousin 1°	No	Normal	None	Yes	No	Collodium baby
19	Venencie (22)	4 y	M	No	No	?	?	Yes	No	Small stature
20	Nanda (20)	19 y	M	No	No	?	None	Yes	No	Intelligence reduction
21	Venencie (21)	14 y	M	No	No	?	Strabism	Yes	No	Epilepsy
22	"	15 y	F	No	No	?	Cataract	Yes	?	Nystagmus
23	Bañuls (13)	52 y	F	Cousin 1°	No	Pathological	?	Yes	Yes	Intelligence reduction
24	Mela (23)	16 y	M	?	No	Normal	?	Yes	No	
25	Wollenberg (4)	16 y	M	Cousin 1°	No	Normal	None	Yes	No	Small stature, small ears
26	Kakourou (16)	8 y	M	No	No	?	Cataract	Yes	No	Improvement on diet
27	Kaassis (24)	11 y	F	No	No	Normal	Strabism	Yes	No	
28	Srebrnik (14)	18 y	M	No	Yes	Pathological	No	Yes	No	
29	"	21 y	M	Cousin 2°	No	Pathological	Strabism	Yes	No	Nystagmus, esotropia
31	Wollenberg	16 y	F	Yes	No	Pathological	?	?	No	Small ears
32	Wollenberg	13 y	M	Yes	No	Pathological	?	?	No	Small stature, small ears

y: years; m: months; d: days; F: female, M: male.

phenotype. Lipid vacuoles inside keratinocytes and peripheral blood granulocytes are the diagnostic hallmark for Dorfman-Chanarin syndrome. Similar vacuoles are seen in another condition, the inherited phytanic acid storage disease named "heredopathia atactica polyneuritiformis" or Refsum's disease. In contrast to the vacuoles found in Dorfman-Chanarin syndrome, lipid inclusions in Refsum's disease can only be seen in the cytoplasm of keratinocytes and melanocytes.

At present there is no known causal therapy for Dorfman-Chanarin syndrome. Intensive symptomatic therapy with oil baths and emollients usually leads to acceptable improvement of the skin changes. A response of gastrointestinal symptoms and, to a lesser extent, muscle weakness to a gluten-free diet has been reported 17 years ago (11). More recently, a low-fat diet poor in long-chain and enriched with medium-chain fatty acids has been reported to improve liver function, liver size and skin manifestations in an 8-year-old boy (16).

The pathogenetic link from a disturbed lipid metabolism to the inflammatory skin phenotype is unknown at present. Since the most common form of ichthyosis, autosomal dominant ichthyosis vulgaris, is known to be associated with atopic dermatitis in about 50% of all patients, we were especially interested in a classification of the erythrodermic component of Dorfman-Chanarin syndrome. Therefore, besides histopathological and ultrastructural examination, the new diagnostic approach of Langerhans' cell phenotyping was performed in 1 of the patients. However, neither skin prick tests nor the highly specific Langerhans' cell phenotyping (6) showed any evidence for an underlying atopic dermatitis (8), suggesting that the inflammation in this disease is due to the gene defect and not to an accompanying atopic dermatitis.

The differential diagnosis of congenital ichthyosis is not an easy one. Depending on the clinical picture, extensive laboratory investigation may be required to confirm the diagnosis. Since in Dorfman-Chanarin syndrome the diagnosis may be easily done by leukocyte analysis, this should be routinely performed in all cases of ichthyotic erythroderma. Electronic cell counters, frequently used for routine leukocyte analysis, are not suitable for detection of the lipid granules, since they will give false negative results (5, 17). Microscopic examination of blood smears must be performed.

A screening of the family members for conductors should be offered, based on clinical relevance and the need for genetic counselling. For conductor identification, microscopic examination of eosinophils has been reported to be useful (17, 18). However, this diagnostic aid has failed in some obligate heterozygotes (5). According to our eosinophil analysis data, this might have been due to the fact that not all of a conductor's eosinophils do contain lipid vacuoles: the 6 conductors investigated from the family described here

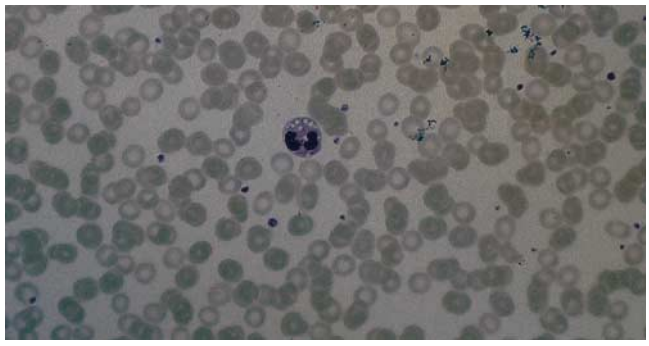

Fig. 5. Eosinophilic granulocyte of a conductor, (Fig. 1, patient III/5), with the diagnostic cytoplasmic lipid vacuoles.

revealed variable percentages of normal and vacuolized eosinophils (Fig. 5), with only 38% total and a minimum of 2/10 positive cells in their blood smears (Table I). Keeping in mind the low occurrence of eosinophils in a normal blood smear (2–4%), the number of 100 leukocytes analysed in a routine setting must be considered insufficient. On the other hand, the low number of eosinophils does not allow for a formal statistical analysis to be performed. Since in our family some conductors had only 2/10 positive eosinophils in their blood smears, we propose the analysis of at least 10 eosinophils as mandatory for a valid conductor investigation in Dorfman-Chanarin syndrome.

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