Ichthyosis, Exocrine Pancreatic Insufficiency, Impaired Neutrophil Chemotaxis, Growth Retardation, and Metaphyseal Dysplasia (Shwachman Syndrome)

Report of a Case With Extensive Skin Lesions (Clinical, Histological, and Ultrastructural Findings)

Marleen Goeteyn; Arnold P. Oranje; Vojislav D. Vuzevski; Ronald de Groot; Lisette W. A. van Suijlekom-Smit

• **The Shwachman syndrome comprises exocrine pancreatic insufficiency, growth retardation, and bone marrow hypoplasia resulting in neutropenia. Clinical, morphological, and ultrastructural studies, as well as hair analysis, were performed in a patient with Shwachman's syndrome and severe ichthyosis. Clinical findings were lamellar ichthyosiform desquamation on the extremities. The hair was scanty and short on the scalp, in the eyelashes, and in the eyebrows. The nails were hyperkeratotic. Morphologic findings were slight, regular acanthosis and severe diffuse hyperkeratosis with variable parakeratosis. The granular layer was thickened. The papillary dermis showed very slight perivascular lymphocyte infiltration. The most prominent ultrastructural finding was the presence of solitary or multiple droplets of varying size in the cytoplasm of the keratinocytes. Hair analysis revealed no abnormalities; the cystine concentration in hair specimens was normal.**

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From the Departments of Dermatovenereology (Division of Pediatric Dermatology) (Drs Goeteyn and Oranje), Pathology (Dr Vuzevski), and Pediatrics (Drs de Groot and van Suijlekom-Smit), Erasmus University and University Hospital Rotterdam, Sophia Children's Hospital, Rotterdam, the Netherlands. Dr Goeteyn is presently with the Department of Dermatology, Ghent (Belgium) University Hospital.

Reprint requests to Department of Dermatovenereology (Division of Pediatric Dermatology), University Hospital Rotterdam, Sophia Children's Hospital, Gordelweg 160, 3038 GE Rotterdam, the Netherlands (Dr Oranje).

In 1964, Shwachman et al[1] described a new clinical entity to which Shwachman's name has remained attached. The syndrome comprises exocrine pancreatic insufficiency, growth retardation, and bone marrow hypoplasia resulting in neutropenia with a cell count below 1500/mm^3. At least 75 cases have been reported.[1-9,18-21]

The most prominent symptoms are (obligate) exocrine pancreatic insufficiency, frequent infections of the lungs and skin, growth retardation, and skeletal abnormalities, in particular, dysplasia of the metaphyses and rib anomalies. Hematologic changes include persistent or intermittent neutropenia and defective chemotaxis.[2-8] The sibship segregation ratios suggest autosomal recessive transmission of the syndrome. Aggett et al[4] documented defective chemotaxis of the neutrophils in asymptomatic parents of patients with Shwachman's syndrome. Neutrophil mobility in these parents had values intermediate between those of the patients and those of the control population, suggesting that they were heterozygous.

In most of the published articles describing cases of Shwachman's syndrome the dermatological problems are of secondary relevance. Skin lesions have been described as ichthyosis or eczema, without proper description or histologic findings.[1-5,9] Skin lesions have not been described in the recent dermatological literature available to us. We describe a patient with Shwachman's syndrome who showed a severe form of ichthyosis. Cutaneous symptoms and histologic findings are emphasized.

REPORT OF A CASE

A boy was born as the fourth child after a pregnancy of

38.5 weeks. The delivery was uneventful. The nonconsanguineous parents have six other healthy children, all female. At the age of 1 month, and again at the age of 3 months, the patient was hospitalized with diarrhea and failure to thrive. At 4 months he was first admitted at Sophia Children's Hospital (Rotterdam, the Netherlands) for further evaluation.

Clinical examination revealed a dystrophic and disproportional child. Exocrine pancreatic insufficiency was diagnosed on the basis of increased excretion of nitrogen, lactic acid, and lipids. Fecal chymotrypsin activity was absent. The diagnosis was corroborated by very low lipase, amylase, and chymotrypsin values found in duodenal fluid. These values hardly rose after pancreozymin and secretin stimulation. A sweat chloride test was repeatedly negative. After establishing the diagnosis of exocrine pancreatic insufficiency, at the age of 5 months, a substitution therapy with pancreatic enzymes and fat-soluble vitamins was started. At 12 years of age, ultrasonography of the pancreas disclosed markedly increased echoes and slight lack of homogeneity. These findings suggest fatty degeneration of the pancreas (S. Robben, MD, Department of Radiology).

Skeletal roentgenograms showed short and broad long bones. The metaphyseal ends were broadened and displayed blurred, irregular scleroses. These bony abnormalities were classified as metaphyseal chondrodysplasia. This metaphyseal chondrodysplasia was most pronounced at the level of the distal metaphyses of the radius and ulna, and both tibial metaphyses. The upper extremities repeatedly showed stress fractures that healed in a faulty position. A Monteggia fracture of the ulna healed with pseudoarthrosis. Calcium, phosphate, vitamin D, and alkaline phosphatase values were repeatedly within normal limits. Growth retardation became more evident with increasing age. The growth rate during the fourth and fifth year of life was less than 2 cm per year. Bone age increasingly lagged behind the chronologic age. The metaphyseal chondrodysplasia did not seem to offer an adequate explanation for the extreme growth retardation. Therefore, growth hormone stimulation tests were performed, which disclosed subnormal secretion of growth hormone. A trial was subsequently started, with intramuscular growth hormone administered twice weekly for 6 months. No growth acceleration resulted and, consequently, this trial was discontinued.

Severe skin and lung infections and recurrent otitis media necessitated frequent hospitalization until the age of 3 years.

Hematologic studies revealed normal red blood cell, platelet, and neutrophil counts. When determined at the age of 1 year, the neutrophil chemotaxis was clearly abnormal (44 μm; normal value, 71 μm $\pm$ 5.2 μm). Chemotaxis proved normal when retested at the age of 12 years. At that time the patient was receiving prophylactic cotrimoxazole treatment. Phagocytosis and intracellular killing of the polymorphonuclear leukocytes were always normal. Chromosomal analysis showed a normal male karyotype.

The parental granulocyte functions were tested; both showed normal chemotactic activity of the neutrophils in response to casein. Phagocytosis and bacterial killing likewise showed no abnormality.

At the age of 14 months the boy developed hydrocephalus, confirmed by computed tomographic scan, and was treated by insertion of a ventriculocardiac drain. An infection necessitated removal of this drain after a few months. Stabilization of the hydrocephalus made a second drainage unnecessary.

Ophthalmologic examination revealed bilateral choked optic discs due to the transient episode of increased intracranial pressure. The teeth were carious, and were repeatedly restored. At the time of this writing, the patient was 12 years old. His length was 86.6 cm (third percentile for Dutch children equals 140 cm) and his weight was 14.1 kg

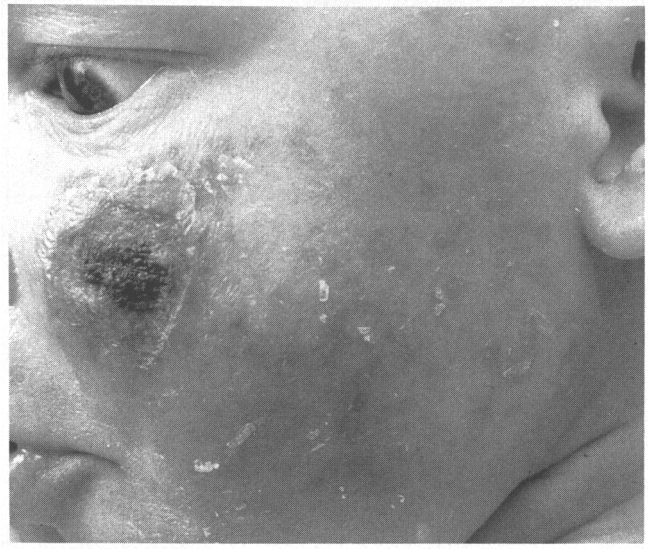


Fig 1.—Ecthyma on the cheek at the age of 3 months.

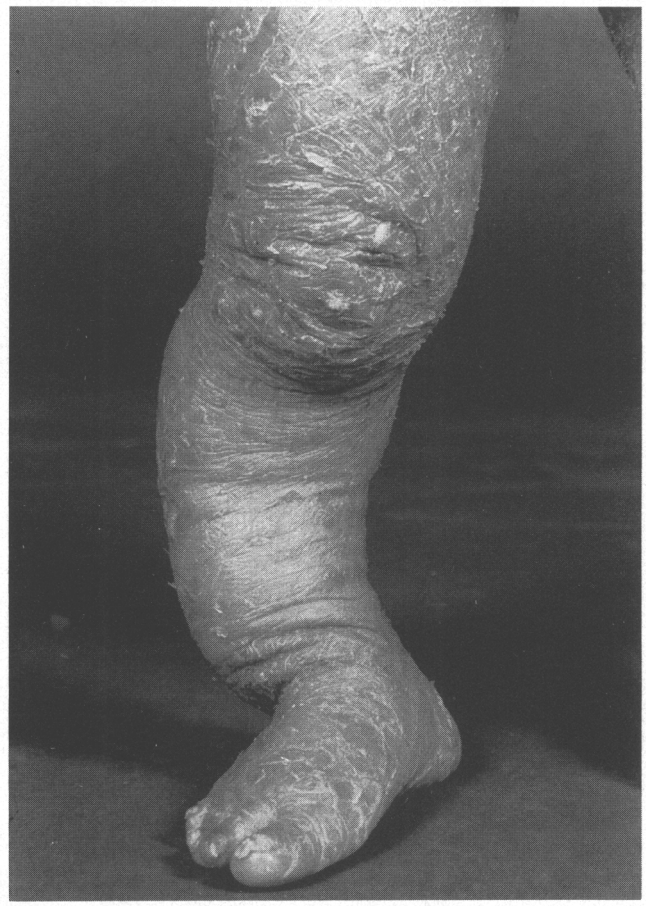


Fig 2.—Lamellar brownish-white desquamations, slight redness of the leg, and hyperkeratosis of the nails at age 12 years. Note the severe deformation of the tibia and the extreme growth retardation.

(normal for his length). Exocrine pancreatic function was completely under control through substitution with pancreatic enzymes and fat-soluble vitamins. Skin and lung infections were prevented by continuous oral administration of cotrimoxazole. Although psychomotor dysfunction was more pronounced in the early years, the patient has attained a subnormal level at the age of 12 years.

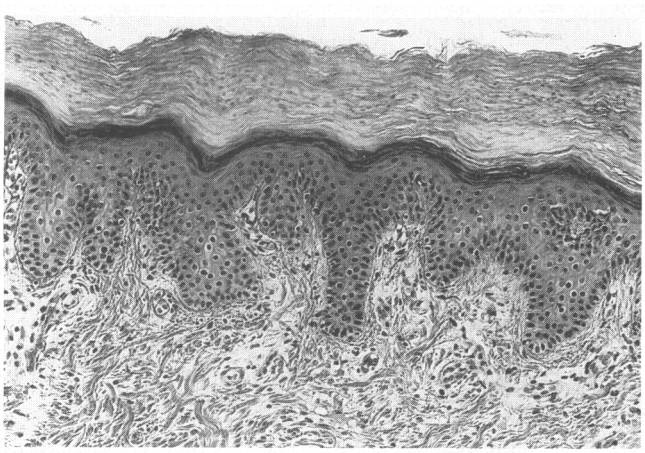


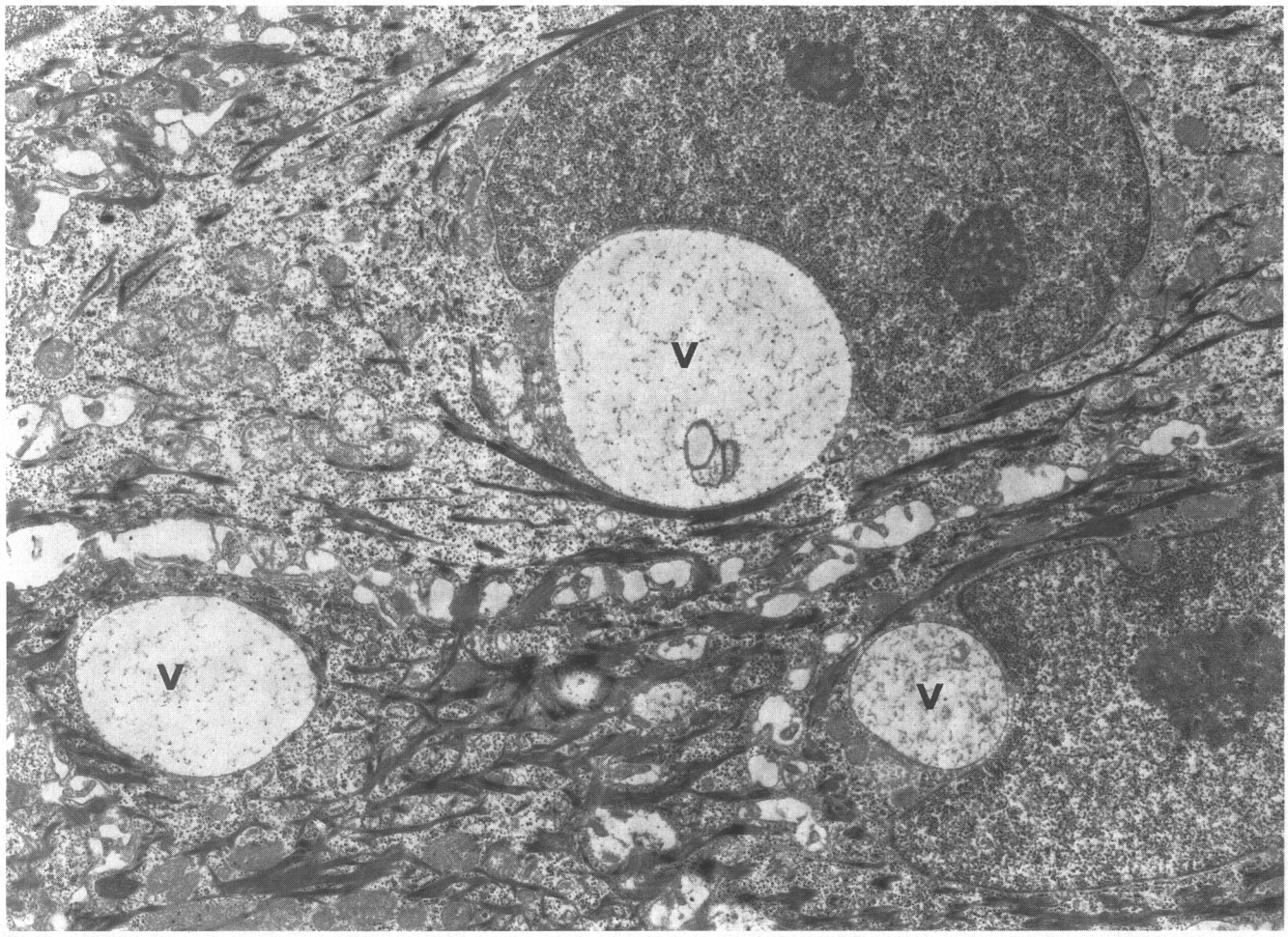
Fig 3.—Epidermis with hyperkeratosis, foci of parakeratosis, and acanthosis. Perivascular lymphocyte infiltration in the papillary corium (hematoxylin-eosin, ×160).

DERMATOLOGIC FINDINGS

At birth there were no skin lesions. After 2 weeks, slight ichthyosiform desquamation developed on the arms and legs. The disorder progressed until there was severe ichthyosiform desquamation and erythema of the extremities. The scalp showed a similar, but less pronounced, development.

Until age 3, the patient had recurrent skin and lung infections with furuncles and ecthyma on the smooth skin (Fig 1) and pyoderma of the toenails. At age 12 years, the dermatologist found lamellar brownish-white desquamations and slight redness of the extremities (Fig 2). The flexural surfaces of the knees and elbows showed a slight redness and scaling. The scales were thinner, whiter, and smaller than in other sites on the extremities. The axillae, the groin, and the neck showed only a thin, white scaling. The palms and soles were hyperkeratotic with fissures and lamellar scales. The trunk showed no redness; there was only fine white scaling. The skin of the face and scalp showed no redness and was covered with fine white scales. On the cheeks and the forehead scattered lamellar scales were present. Ectropion was absent. The scalp hair was scanty with short, thin, colorless hairs. The eyelashes and eyebrows were likewise scanty. The nails of the hands and feet showed marked hyperkeratosis.

Fig 4.—Large droplets in the cytoplasm of keratinocytes (v) (electron microscopy, ×4400).



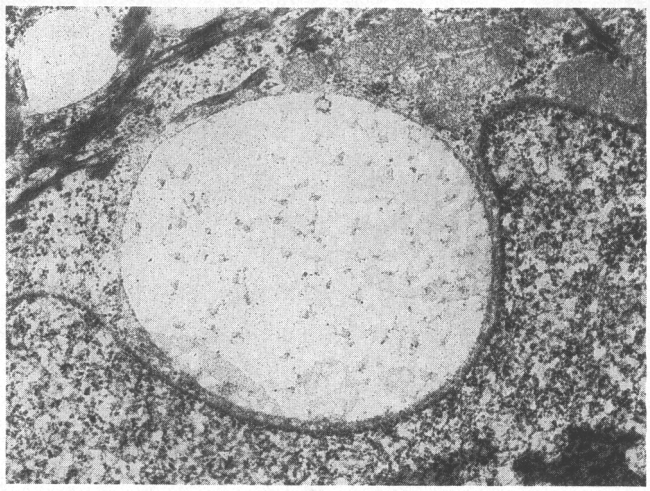


Fig 5.—Detail of a droplet in a keratinocyte showing fine granular material (electron microscopy, ×12 000).

HISTOLOGIC FINDINGS

In a biopsy specimen of a skin lesion of the leg the epidermis showed slight, regular acanthosis with marked hyperkeratosis and foci of parakeratosis. The granular layer was clearly increased (Fig 3). Cytoplasmic droplets observed by electron microscopy were not evident on light microscopy. Sparse perivascular lymphocyte infiltration and edema were present in the papillary corium.

ELECTRON MICROSCOPIC FINDINGS

Ultrastructurally, the cells of the stratum spinosum were closely attached to each other. Desmosomes appeared normal (in figure and number) in the intercellular spaces. Attached tonofilaments were short in size. In the cytoplasm, mitochondria, Golgi apparatus, endoplasmic reticulum, and glycogen granules were seen. Occasionally, the cytoplasm contained round or oval dropletlike structures of varying sizes (Fig 4). These droplets were not surrounded by a membrane. Their contours were smooth and they contained a fine granular material (Fig 5).

The cells of the granular layer frequently contained small inclusions that were round or oval in shape and 200 to 300 nm in size. These inclusions were either electron optically empty or they contained a small amount of fine granular material. Similar, but smaller, inclusions were present in the cells of the cornified layer. The cytoplasm of the granular layer cells contained keratohyaline granules and small vacuolelike structures of approximately the same size as lamellar bodies. In these vacuolelike structures, disclike structures were sometimes recognizable. However, they were sometimes empty, lacking normal structures. The mitochondria were poorly preserved. We cannot draw any conclusions about the lamellar granules, although they look partly degenerated.

HAIR ANALYSIS

Light-microscopic examination revealed hairs of small, varying diameter. Hair-shaft abnormalities (trichoschisis and trichorrhexis nodosa) were seen sporadically. With polarizing light no abnormalities were visible. The cystine concentration of the hair was normal (Dr Leynse, Delta Hospital, Poortugaal/Rotterdam).

Most Common Features of Shwachman Syndrome: Comparison Between Data From Literature and the Described Case

Most Common Features of Shwachman Syndrome	Aggett et al[3,4] (n = 21)		Savilahti and Rapola[5]/ Ruutu et al[6] (n = 16)		Present Case*
	No.	%	No.	%	
Exocrine pancreatic insufficiency	21/21	100	16/16	100	+
Severe infections	17/21	81	12/16	75	+
Recurrent respiratory infections	12/21	57	4/8	50	+
Otitis media	8/21	38	7/8	88	+
Recurrent skin infections	Many	...	...	...	+
Hematological changes					
Neutropenia	19/21	90	13/16	81	−
Abnormal neutrophil chemotaxis	12/14	86	8/8	100	+
Thrombocytopenia	14/21	67	4/13	31	−
Anemia	10/21	48	7/16	44	−
Bone marrow hypoplasia	6/6	100	...	...	Unknown
Growth retardation (−P3)	20/21	95	15/16	94	+
Skeletal changes	21/21	100	8/8	100	+
Metaphyseal dysplasia	13/21	62	8/8	100	+
Rib anomalies	11/21	52	...	...	−
Clinodactyly	10/21	48	...	...	−
Abnormal tubulation	...	...	...	...	...
Long bones	7/21	33	...	...	+
Skin lesions					
Ichthyosis	13/21	62	7/16	44	+
Liver changes					
Transient hepatomegaly	11/21	52	...	...	−
Transient increase in transaminases	11/21	52	10/12	83	+
Fatty infiltration	6/6	100	5/8	63	Unknown
Psychomotor retardation	14/16	88	...	...	+
Diminished IQ	6/9	67	...	...	−

*Plus sign indicates present; minus sign, not present.

REVIEW OF THE LITERATURE

In recent literature, the clinical symptoms of the syndrome have been discussed and presented mainly in two series of patients. The most common symptoms observed in these two series are listed in the Table. With each symptom, its presence or absence in our patient is marked with a plus or minus sign.

In the first series, Aggett et al[3] gave a detailed description of 21 patients, all of whom showed exocrine

pancreatic insufficiency and skeletal abnormalities of varying nature and severity. Neutropenia was frequently found, but was absent in two patients. In 12 of 14 patients, neutrophil chemotaxis was disturbed (two of these 12 patients showed no neutropenia). All patients except one were below the third height percentile. Severe infections were recorded in 17 patients, with respiratory tract and skin infections as well as otitis media as the most common findings. The severity and frequency of the infections diminished with increasing age. Skin lesions were found in 62% of the patients. The skin abnormalities were described as an ichthyotic maculopapular rash affecting the entire body, with the face, scalp, and trunk being more severely involved.[3]

The second series, presented by Savilahti and Rapola,[5] consisted of 16 patients. In eight patients, the diagnosis was established at autopsy after death due to myocardial insufficiency. All patients in these series showed exocrine pancreatic insufficiency; eight were examined for skeletal anomalies and all showed metaphyseal chondrodysplasia. Growth retardation (height below the third percentile) was seen in 94% of the cases. Objective evidence of neutropenia was obtained in 13 patients. Eight neutropenic patients were tested for functional neutrophil defects, and all showed defective chemotaxis.

Recurrent severe infections were found in 12 cases. The infection was specified in eight cases: seven of the eight patients have had severe otitis media at least once, four of the eight patients have had recurrent respiratory tract infections. Skin lesions were present in 44% of the cases. The lesions were described as varying from severe ichthyosis to slight scaling of the skin. One pair of siblings had very severe ichthyosis. The skin lesions tended to improve with age. Only scaling and dry skin were present after 2 years of age in all except for one girl who had severe ichthyosis in infancy.

In the original description of Shwachman's syndrome, skin lesions were found in two of six patients.[1] In the first case, the skin was covered by a generalized erythematous scaly rash that appeared worse on the flexor surfaces of the knees and elbows. In the second case, a generalized erythematous scaly eruption was present over the head, face, hands, feet, and trunk. The eruption was most marked on the flexural surfaces of the arms and legs. Dopfer et al[9] described a dry, scaling, erythematous skin disorder in a 1-year-old girl with Shwachman's syndrome.

COMMENT

The various clinical features encountered in our patient are quite consistent with the Shwachman syndrome. They were as follows: exocrine pancreatic insufficiency; extreme growth retardation with dysplasia of the metaphyses, disturbed neutrophil chemotaxis at an early age, and ectodermal defects like ichthyosis, dysplastic hairs, and dystrophic nails and teeth.

Possibilities to be considered in the differential diagnosis are Tay syndrome, cartilage hair hypoplasia syndrome (McKusick-type metaphyseal chondrodysplasia), and neutral lipid storage disease (Chanarin-Dorfman syndrome). Moreover, we have to consider the possibility that the skin lesions may be secondary to the patient's pancreatic insufficiency.

The Tay syndrome is characterized by ichthyosis with large scales, hyperkeratosis, and fissures on the hands and feet.[10] Other symptoms are nail dysplasia, hypoplasia of subcutaneous tissue, progerialike face, small height (below the third percentile), and hypogonadism.[10] Mental retardation has been reported in all cases. An important diagnostic sign is trichothiodystrophy, a hair anomaly characterized by thin, fragile, and sparse hairs. Trichoschisis and trichorrhexis nodosa are the corresponding hair-shaft abnormalities. Polarizing light microscopy reveals a typical phenomenon of alternate white and black bands, known as the zebra effect. Biochemically this defect results from a low cystine concentration in the hairs. The nails also show cystine deficiency. In our patient we could not find microscopic and biochemical signs of trichothiodystrophy. This rules out Tay syndrome.

The cartilage hair hypoplasia syndrome is characterized by micromelic dwarfism; metaphyseal dysplasia; fine, fragile, thin hairs on the scalp, eyelashes, and eyebrows; small pudgy hands and feet; hyperlaxity of joints; and depressed lymphocyte proliferation.[11,12] Only the hair abnormalities and metaphyseal dysplasia found in our patient could fit into this syndrome, and, consequently, this diagnosis was likewise ruled out.

Neutral lipid storage disease (Chanarin-Dorfman syndrome)[13] is characterized by congenital ichthyosis, deafness, cataracts, myopathy, fatty liver, and central nervous system disorders. Short stature has been reported in only a few cases. An important diagnostic feature is the presence of lipid droplets within the cytoplasm of circulating leukocytes and in the epidermis. These droplets can be demonstrated by a blood smear and by light-microscopic examination of a skin biopsy specimen. In our patient we could not find these lipid droplets either in a blood smear or on light-microscopic examination of a skin lesion biopsy specimen. In our case, dropletlike structures in the keratinocytes were only visible on electron microscopy. Mostly, they were not electron lucent, as in Chanarin-Dorfman syndrome, but contained a fine granular material.

In states of extreme deprivation a clinical syndrome of essential fatty acid deficiency (EFAD) develops as illustrated in experimental animal studies.[14] The EFAD has been described in infants suffering from chylous ascites who were maintained on low-fat diets, and in patients with fat malabsorption as a result of massive intestinal resection who were maintained by intravenous feeding.[14,15] In some cases of EFAD, a dry, scaly, erythematous dermatitis has been reported.[14,15] We did not expect EFAD in our patient because the symptoms of fat malabsorption disappeared after substitution with pancreatic enzymes and fat-soluble vitamins. Therefore, we did not study the fatty acid ratio, nor did we supplement

linoleic acid by trial. Also, in other diseases with exocrine pancreatic insufficiency (eg, cystic fibrosis), EFAD has not been reported.

Some of the data argue against the diagnosis of Shwachman's syndrome. The growth retardation in our patient was more pronounced than usually described; the same probably applies to the extensive skin disorder. Hematologic changes were minimal; despite repeated determinations neutropenia was not established and previously defective chemotaxis had been normalized. Only Savilahti and Rapola[5] reported severe ichthyosis in two patients with extreme growth retardation.

We cannot explain why neutropenia was not detected in our patient. In some instances it might be explained by a concomitant infection. Patients with Shwachman's syndrome are indeed known to elevate their neutrophils to normal values during infectious episodes.[3,6] We performed neutrophil counts during clearly defined noninfectious periods, but were unable to demonstrate neutropenia.

Although no neutropenia was detected in our patient, chemotaxis of the polymorphonuclear leukocytes was disturbed at an early age. Defective neutrophil chemotaxis is quite common in the Shwachman syndrome,[4-6] and neutrophil function may be defective without neutropenia.[4] The impaired chemotaxis is probably based on a defect in the cytoskeleton (microtubules and microfilaments) of the neutrophils.[16] Normalization of the neutrophil function with advancing age has not been reported. On the contrary, Ruutu et al[6] demonstrated the constant character of the disturbed chemotaxis.

Despite the absence of neutropenia and the improved chemotaxis, the presence of exocrine pancreatic insufficiency is a strong argument for the diagnosis of Shwachman's syndrome. Other than cystic fibrosis and Shwachman's syndrome there are practically no disorders in children that lead to pancreatic insufficiency. The normal sweat chloride test ruled out cystic fibrosis. Therefore, we concluded that our patient was suffering from Shwachman's syndrome.

The skin findings in patients with cystic fibrosis include maculopapular rash, erythema nodosum, rheumatoid nodules, urticaria, purpura, and vasculitis.[17] Ichthyosis has not been reported.[17]

In Shwachman's syndrome, skin lesions are present in ±50%[2,3,5] of the cases. These lesions have been described as mostly ichthyosiform.[3,5,6] The predilection sites may differ, but erythema and a variable degree of scaling are always present. Although differences in severity and localization occur, the literature[1-3,5,6,9] suggests that ichthyosiform skin lesions are a feature of the syndrome. The Shwachman syndrome can be included in the list of syndromes in which ichthyosis occurs. Whether the clinical and histologic skin abnormalities, as described in our case, are specific for Shwachman's syndrome, will become evident from further dermatologic descriptions in other case reports.

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