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Case Report

Shwachman's Syndrome and Leukaemia

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Summary. The clinical and morphological characteristics of Shwachman's syndrome (exocrine pancreatic insufficiency, pancytopenia, skeletal changes) were observed in a boy who, at the age of 8 years, developed a juvenile form of chronic myeloic leukemia which did not respond to cytostatic treatment. Autopsy revealed a striking lipomatous atrophy of the pancreas, defects in the ossification zones of the bones and marked dwarfism. In addition there was leukaemic infiltration of the pancreas, the spleen, the liver and the lymph nodes. The association of Shwachman's syndrome with leukaemia is a rare, but remarkable complication of this entity because of its relationship to the preceeding pancytopenia. Thorough follow-up of the haematological status of patients with Shwachman's syndrome is recommended.

Key words: Shwachman's syndrome – Leukaemia – Pancreatic atrophy.

Introduction

The syndrome of exocrine pancreatic insufficiency in childhood is either caused by cystic fibrosis or by a rare form of pancreatic atrophy. While cystic fibrosis has been recognized for many years (Landsteiner, 1905; Andersen, 1938; Bodian, 1952; Seifert, 1956; Andersen, 1963; Oppenheimer and Esterly, 1973; Dehner, 1975; Kissane, 1975; and others), the characteristics of non-fibrous atrophy have only been established in the last 20 years (Shwachman et al., 1964; Bodian et al., 1964; Burke et al., 1967). Prior to the introduction of special diagnostic procedures, non-fibrous atrophy of the pancreas was only diagnosed at autopsy when a lipomatous organ was found with severe atrophy of the exocrine parenchyma. Seifert (1959) compiled 15 cases of lipomatous atrophy from the literature, adding 2 of his own.

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A particular entity which includes exocrine pancreatic insufficiency, diagnosed by finding lipomatous pancreatic atrophy, in association with bone marrow dysfunction and skeletal disorders, was first described by Shwachman and coworkers (1963, 1964) and Bodian and coworkers (1964). By 1977, some 100 cases of the so-called Shwachman's syndrome had been observed (Lebenthal and Shwachman, 1977). The haematological disturbances of the syndrome include neutropenia, anemia and thrombocytopenia, and it is of interest that in three cases they were followed by a leukaemia (Nezeloff and Watchi, 1961; Huijgens et al., 1977; Strevens et al., 1978).

In this report we present another case of Shwachman's syndrome associated with leukaemia.

Clinical History

U.B., a boy, was admitted to hospital at the age of eight weeks because of infantile spastic-hypertrophic pyloric stenosis which was treated medically. Both parents and an elder sister were healthy.

At that time an exocrine pancreatic insufficiency, with steatorrhoea and markedly reduced activities of trypsin and amylase in the duodenal fluid, became manifest. Cystic fibrosis was excluded by repeatedly normal sweat tests (pilocarpine iontophoresis). Since in addition to exocrine pancreatic insufficiency the patient showed neutropenia (neutrophil count 0.18×10^9 per litre) and anemia, Shwachman's syndrome was diagnosed.

Pancreatic enzyme substitution and multiple transfusions improved the patient's condition but his growth rate remained retarded. During the first few years of his life, the boy suffered from recurrent infections of the respiratory tract and the skin, and he was hospitalised once or twice a year. Hepato-splenomegaly occurred together with high serum transaminases when the boy was 12 months of age. Needle biopsy of the liver showed hepatitis with periportal fibrosis and activation of Kupffer's cells. HB_sAg was negative in the serum. Bone marrow aspiration showed a preponderance of juvenile forms of myeloid cells and toxic granulation. X-ray examination of the bones revealed multifocal metaphyseal dystostosis with central excavations of the metaphyseal plates of proximal femur, distal femur and proximal tibia, distal radius and ulna and of the ribs. At the age of three years thrombocytopenia appeared with the signs of a haemorrhagic diathesis. Bone marrow aspiration at that time was nearly normal except for hypoplastic megakaryocytes.

Five weeks before his death the boy, now aged eight years and four months, was admitted to Hamburg's university hospital with severe nasal and gingival bleeding, petechiae and a haematoma of the lower leg. Liver and spleen were palpable one and a half hands breadths below the costal margin. There was considerable abdominal distension and multiple enlarged lymph nodes could be palpated. The boy showed severe anaemia and stunting of growth (length 121 cm and weight 22.0 kg – below the third percentile).

Laboratory Investigations

Haemoglobin 10.8 g per dl. Reticulocyte count 4.2% total RBC. Total WBCs 77.5×10^9 per litre. Platelet count 22.0×10^9 per litre. Films of peripheral blood showed 33% atypical blast cells. Fetal transformation of erythropoesis with 15% HbF-cells and raised activities of red cell enzymes. Bone marrow aspiration exhibited 67% atypical blast cells with cytochemical characteristics of monoblasts. Philadelphia chromosome negative.

Serum electrolytes, calcium, phosphate, and alkaline phosphatase normal. Total serum proteins 54 g/l. Albumin 26 g per litre. Serum IgM low (0.31 g/l). Transferrin low (1.58 g/l). Other immunoglobulins and alpha-1-antitrypsin normal. Serum transaminases slightly raised. Mononucleasis serology negative.

The diagnosis of juvenile chronic myeloic leukaemia was based on the haematological data. Two therapeutic cycles of podophyllin together with high dose corticosteroids failed to produce a remission. The boy developed severe thrombocytopenia and anaemia notwithstanding numerous transfusions. He died of profuse gastrointestinal bleeding.

Autopsy Findings

(S.-Nr. 665/78, Institute of Pathology University of Hamburg)

Pancreas. Grossly the pancreas appeared enlarged, due to pseudohypertrophy because of the striking replacement of exocrine parenchyma by fatty tissue (Fig. 1).

On histology only a few acini and a small number of ducts remained in the fatty tissue, which was focally infiltrated by immature myeloic cells (Fig. 2). The ducts showed no mucous distension. The islets of Langerhans appeared to be normal in their cytological composition and number.

Skeletal System. The patient was too small for his age.

Gross observation of the spongiosa of the femoral neck revealed an irregular structure of the ossification lines and a slight rarefication.

The histological examination of the bone was done on material which had not been decalcified (Delling, 1975). In the proximal and distal part of the femur there was an irregular configuration of the growth zone. In the primary opening zones there were amorphous precipitates of calcium salts. The reconstruction surfaces were reduced. The osteoid was not augmented in the spongiosa

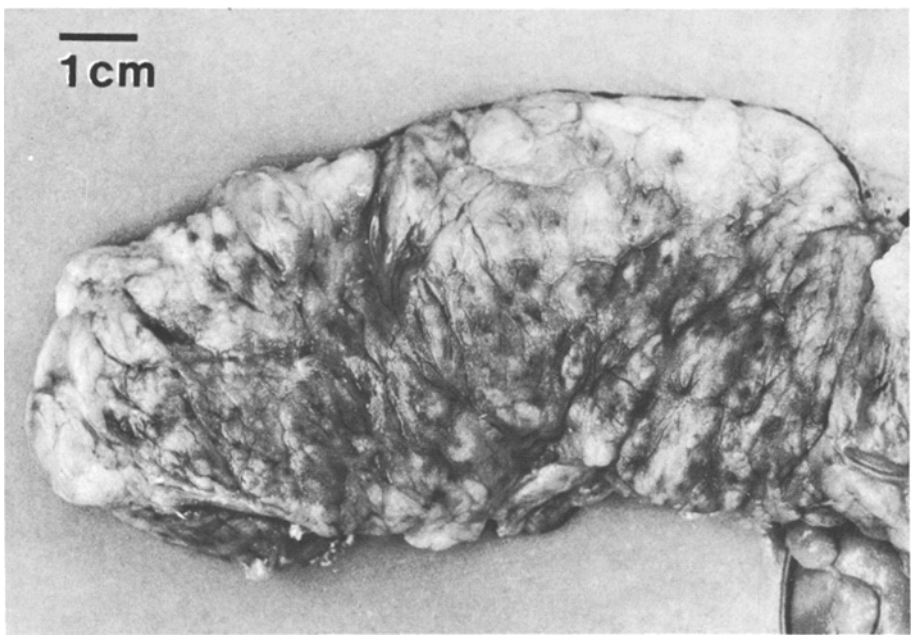

Fig. 1. Gross appearance of the pancreas. Enlargement of the whole organ by fatty tissue

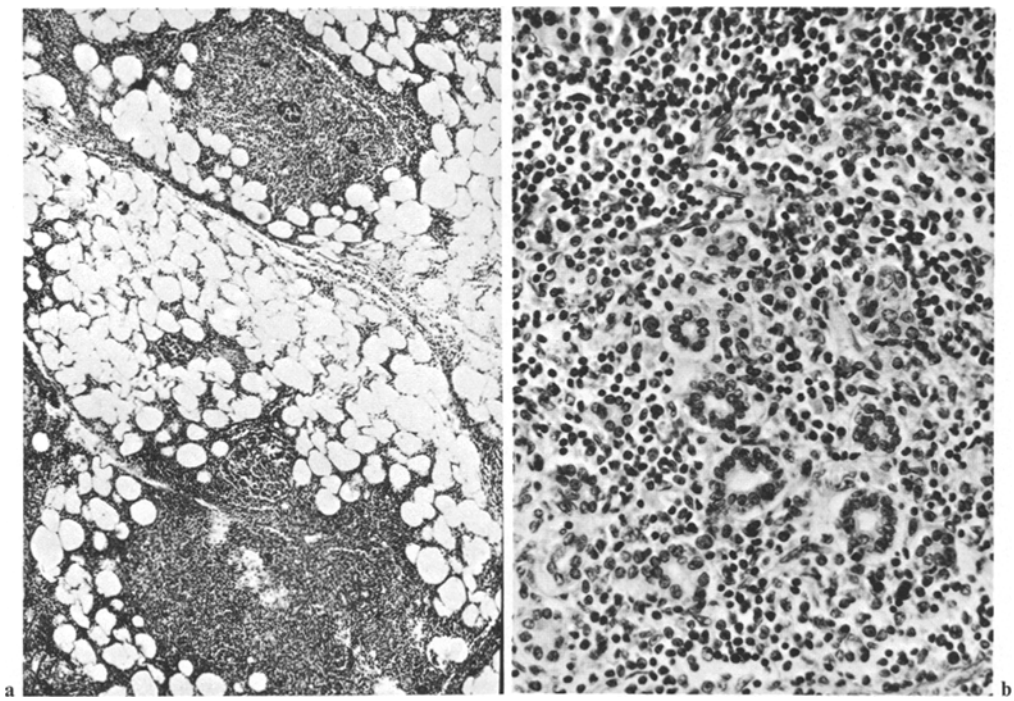

Fig. 2. a (Magnification ×60), **b** (Magnification ×300). Replacement of the exocrine pancreatic tissue by fatty tissue. Some rudiments of acinous and tubular structures. No mucous distension of the ducts. Infiltration by leukemic cells. Normal islets of Langerhans. PAS-staining

(Fig. 3a). The bone marrow was impressively infiltrated by immature myeloid cells, the erythropoesis and thrombopoesis being reduced (Fig. 3b). The bone of the pelvis and the vertebra showed similar alterations. In the vertebra there was a fibrosis of the marrow in some regions.

Lymphatic System. All lymph nodes were enlarged, showing a gray surface. Histologically, their follicular structure was destroyed by infiltrates of immature myeloic blasts.

Macroscopically, the spleen was strikingly enlarged. The histology was similar to that observed in the lymph nodes.

Liver. The liver was moderately swollen and had a yellowish colour. There were some punctate haemorrhages under the capsule. Histologically there was a blastomatous infiltration of the portal tracts and of the sinuses by myeloid cells. Some hepatocytes showed fatty degeneration.

Intestines. There was profuse bleeding in the whole gastrointestinal tract. Histologically, the lamina propria and the submucosa of the intestines were infiltrated by myeloic cells which appeared to be immature.

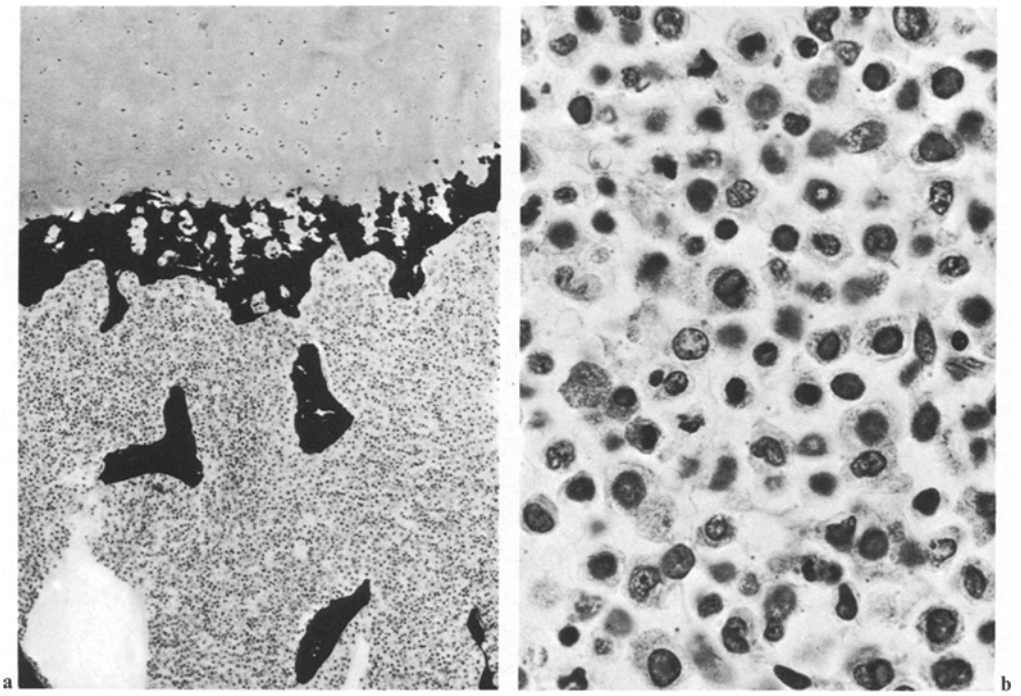

Fig. 3. a (Magnifikation ×75), **b** (Magnification ×400). Undecalcified material. Irregularities of the growth zone. Amorphous precipitates of calcium salts. Infiltration by leukemic cells. Kossa's staining

Parotid Gland. The parotid tissue showed some atrophic acini. The interstitial spaces were infiltrated by immature myeloid cells.

The signs of a haemorrhagic diathesis were prominent. Besides massive gastrointestinal bleeding, there were some petechial haemorrhages in the subendocardial regions of the heart, in the subpleural regions of the lungs and in the subcapsular spaces of the liver.

The patient died of the profuse gastrointestinal bleeding.

Discussion

This case presents all features of the so-called Shwachman's syndrome with exocrine pancreatic insufficiency, dwarfism, metaphyseal changes and severe bone marrow dysfunction (Shwachman et al., 1964; Bodian et al., 1964; Burke et al., 1967; Lebenthal and Shwachman, 1977).

The pancreatic insufficiency resulted from an almost complete replacement of the acinar pancreatic parenchyma by fatty tissue, leaving only the ducts and islets of Langerhand unaffected. Severe lipomatous atrophy of the pancreas in children had been observed some time before Shwachman and coworkers (1963, 1964) first described the syndrome of exocrine pancreatic insufficiency

and bone marrow dysfunction. Seifert (1959), analysing 15 cases in the literature together with 2 of his own, established lipomatous atrophy of the pancreas in children as a distinct entity on morphological grounds, the most prominent features being the almost total replacement of the exocrine pancreas by fatty tissue without any inflammatory reaction. Lipomatous atrophy of the pancreas is seen in less than 0.1 percent of autopsy cases in children. In another retrospective study Bodian and collaborators (1964) found 18 cases in which the symptoms and pancreatic changes were consistent with the diagnosis of Shwachman's syndrome. Hadorn (1972) showed that the exocrine pancreatic insufficiency results from a gross reduction of the output of all pancreatic enzymes and bicarbonate secretion.

Apart from the pancreatic changes an important feature of the Shwachman's syndrome is the metaphyseal change in the hips, especially in the femoral necks, and to a lesser degree changes in the ribs, the knees and wrists (Burke et al., 1967; Shmerling et al., 1969). While Shwachman and associates (1964) did not mention bone alterations, other authors later described the skeletal changes which may be part of the complete picture of this syndrome (Burke et al., 1968; Giedion et al., 1968). Shmerling and coworkers (1969) observed zones of rarefication and condensation near the ossification line of the femoral necks. These changes led to a more or less severe destruction of the femoral necks. Taybi and associates (1969) separated their case from other forms of metaphyseal disorders such as the Jansen type, the Schmid type, the Spahr type, the spondometaphyseal type and the Mc Kusick's syndrome on the basis of radiological examinations.

In our undecalcified material the morphological lesions underlying the radiological findings were identified as an irregularity of the ossification line with amorphous deposits of calcium salts.

Giedion and coworkers (1968) discussed the possible relation of the metaphyseal changes to the pancreatic atrophy. In their opinion, the pancreatic malfunction may only be a supplementary factor in the pathogenesis of the bone defects. His arguments are: firstly, these bone disorders are localized ones, secondly there is generally no disturbance of the calcium and phosphate metabolism in Shwachman's syndrome, thirdly there is no bone disorder in cystic fibrosis (Shmerling et al., 1969). Although there are some reports of spontaneous healing (Giedion et al., 1968) of the metaphyseal changes, there does not seem to be a marked improvement following treatment with pancreatic enzymes.

Dwarfism, with a growth rate below the 3rd percentile, is a common finding in Shwachman's syndrome (Shmerling et al., 1969; Hadorn, 1972; Beyreiss, 1974). Although the reduced height may be explained by the alterations of the femoral necks in some cases, there is general agreement that there is an additional underlying cause of the dwarfism. Giedion and coworkers (1968) suggest that malnutrition due to pancreatic insufficiency may lead to dwarfism. However, Lücking and Grüttner (1972) who reported a case with distinct dwarfism, suggest that growth retardation was probably not caused by pancreatic insufficiency alone, since in their case enzyme substitution cured the malnutrition but did not improve the growth rate.

Bone marrow dysfunction, one of the leading features of Shwachman's syndrome, mostly appears as neutropenia (Hadorn, 1972). The hypocellular bone marrow shows a so-called arrest of maturation of neutrophils (Shwachman et al., 1964). This is frequently associated with hypoplastic anaemia and/or a thrombocytopenia, which is associated with repeated infections. In our case the bone marrow defects were finally followed by a juvenile form of chronic myeloic leukaemia characterized by an elevated level of HbF. Although elevated levels of HbF have occasionally been reported (Shwachman et al., 1964), the coincidence of Shwachman's syndrome and leukaemia has rarely been observed. Nezeloff and Watchi (1961) observed a case with monocytic leukaemia, which was preceded by a Shwachman's syndrome (Bodin et al., 1964; Streven et al., 1978). Huijgens and coworkers (1977) observed a 23 year old patient with Shwachman's syndrome who developed an acute myeloblastic leukaemia which was preceded by a sideroblastic anaemia and an acquired form of the Pelger-Huet anomaly, observations which may be interpreted as "pre-leukemic" (Saarni and Linman, 1973; Wintrobe et al., 1975; Huijgens et al., 1977). Strevens and coworkers (1978) reported a case of a 14 year old boy who developed an acute lymphoblastic leukaemia. The relationship between Shwachman's syndrome and the occurrence of leukaemia remains obscure. However, these observations point to a general defect of the bone marrow function. Moreover, they emphasize the necessity for continuous examination of haematological variables in patients with Shwachman's syndrome, in order to detect a leukaemia soon after its onset.

In view of the fact that in several families more than one child was affected by the disease, the underlying cause of Shwachman's syndrome is generally thought to be a genetic defect transmitted as an autosomal recessive one (Lebenthal and Shwachman, 1977).

A possible intrauterine cause has been discussed since the sensitive periods of the development of the pancreas and the bone marrow are both at the fifth month (Shwachman et al., 1964). However, no evidence in support of this assumption has been provided to date.

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