Virchows Archiv A Pathol Anat (1990) 417:247–253

Virchows Archiv A
Pathological Anatomy and Histopathology

Dyskeratosis congenita (Zinsser-Cole-Engman syndrome)

An autopsy case presenting with rectal carcinoma, non-cirrhotic portal hypertension, and *Pneumocystis carinii* pneumonia

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Received December 1, 1989 / Received after revision February 12, 1990 / Accepted February 19, 1990

Summary. A 24-year-old Japanese man presented with dyskeratosis congenita (DC, Zinsser-Cole-Engman syndrome) complicated by non-cirrhotic portal hypertension, signet ring carcinoma of the rectum and *Pneumocystis carinii* pneumonia. At the age of 9 years, he was diagnosed as having DC on the basis of typical clinical manifestations including atrophic lingual papillae, hyperpigmentation of the skin, thrombocytopenia, and ophthalmological abnormalities. A few years later pancytopenia and splenomegaly developed. At 24 years, signet ring carcinoma of the rectum was detected but could not be resected because of the severity of the pancytopenia. Death was due to respiratory failure from *P. carinii* pneumonia. At autopsy the case illustrated several unique findings for DC, including non-cirrhotic portal hypertension, atrophy of frontal lobe and markedly slender folia of the cerebellum and superimposed infections with herpes zoster virus and *P. carinii*. Striking lymphocyte depletion and atrophy of lymphoid parenchyma in lymph nodes, tonsils, spleen, gastrointestinal tract, or thymus were seen histologically. The morphological picture supports the suggestion that there is a defect in the cell-mediated immune system in patients with DC, although immunoglobulin levels in the blood are normal. The cell-immune deficiency is a major factor in the poor prognosis.

Key words: Dyskeratosis congenita – Signet ring carcinoma of the rectum – Non-cirrhotic (idiopathic) portal hypertension – *Pneumocystis carinii* pneumonia – Immunodeficiency

Introduction

Dyskeratosis congenita (DC, Zinsser-Cole-Engman syndrome) is an extremely rare congenital multisystemic disorder, characterized by the triad of reticular pigmentation of the skin, dystrophic nails, and leucoplakia of the mucous membranes. It is often associated with severe pancytopenia and a predisposition to malignant tumours (Sirinavin and Trowbridge 1975; Davidson and Connor 1988). Additionally, other minor abnormalities involving the eyes, ears, teeth, oesophagus, bone, liver, or endocrine organs have been noted. Recently, several reports describing the immunodeficiency associated with DC have appeared in the literature (Inoue et al. 1973; Trowbridge et al. 1977; Fudenberg et al. 1979; Giannetti and Seidenari 1980; Wiedemann et al. 1984; Ling et al. 1985). We have had the opportunity to examine an autopsy case with DC in a man aged 24, who suffered from non-cirrhotic portal hypertension and signet ring carcinoma of the rectum. Ultimately this patient died of a profound respiratory failure due to *Pneumocystis carinii* pneumonia. In previous reports the majority of the cases have been reported in the dermatological literature, while generalized histopathological information is scanty. In this paper, we present autopsy findings of a single case with DC and emphasize the immunodeficiency as a major component of DC.

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Case report

The patient was born of a full-term pregnancy, and weighed 2080 g. He seemed entirely well until the age of 3 years, when atrophy of the lingual papillae was noted. Dermatological findings, first noted when the patient was 4 years of age, consisted of diffuse reticular pigmentation of the skin of the neck, particularly around the ear and dystrophic changes of the finger and toe nails. At the age of 9 years, he was admitted to another hospital for evaluation of the dystrophic nails and atrophic lingual papillae, where he was diagnosed as having DC. The prominent features included atrophy of lingual papillae, reticular pigmentation of the skin, dystrophic nails, thrombocytopenia (ranging from 30000 to 60000/mm^3), ophthalmological abnormalities manifested by a reduction in visual acuity, narrow visual fields, mild atrophy of optic fundi, and delayed light reflexes, as well as mild mental retardation. Chromosomal studies showed a normal 46 *XY* karyotype. There was no family history of hereditary disorders.

Over the ensuing several years dermatological abnormalities were slowly progressive, but no other abnormalities developed. Between the age of 12 and 14, a haemorrhagic tendency was noticed. At 21 years of age, he was admitted to Division of Haematology in our hospital for evaluation of pancytopenia and splenomegaly. On examination the spleen edge was palpated 2.5 finger-breadths below the left costal margin, but the liver was not felt. Significant laboratory findings included: WBC count, 1300/mm^3 with 40% neutrophils, 1% band forms, 6% eosinophils, 1% basophils, 49% lymphocytes, and 3% monocytes; haemoglobin 9.5 g/dl; RBC count 243×10^4/mm^3; haematocrit 27.4%; mean corpuscular volume (MCV) 112 μm^3/cell; platelet count 70000/mm^3; serum immunoglobulin levels within normal ranges; cholinesterase 5 IU/ml; vitamin B_{12} 300 pg/ml (normal, 300–1000). A test for hepatitis B surface antigen and surface antibody was negative. An upper gastrointestinal series disclosed mild oesophageal varices but no tumour.

A radionuclide scan of the liver and spleen showed moderate enlargement of the spleen, with an increased uptake of the radionuclide; the liver appeared mildly shrunken, with poor uptake and no focal defect; the bone marrow showed mild uptake of activity; these findings were interpreted as consistent with hepatic cirrhosis.

Six months before final admission he complained of chronic constipation and was admitted to hospital for evaluation. On examination there was dystrophy of all of the nails and reticular hyperpigmentation with depigmented spots of almost all the skin was present. No lymphadenopathy was found. Abdominal examination revealed pronounced distension of the abdomen with weak bowel sounds; the spleen, the liver or masses were not palpated. A colonoscopic examination disclosed circumferential stenosis of the lower rectum, 7 cm in length, with irregularly shaped ulcerations, consistent with an appearance of an infiltrating scirrhous carcinoma. Microscopical examination of the biopsy specimens of the rectum disclosed an infiltrating poorly differentiated adenocarcinoma composed of signet ring cells. A CT scan of the abdomen showed no metastasis in the liver. A fiberoptic oesophagus-gastroscopic examination revealed unremarkable changes except for mild oesophageal varices. On the 27th hospital day a colostomy was performed. Soon thereafter fever and dyspnoea developed. An *X*-ray film of the chest showed bilateral diffuse ground glass densities. Ultimately, the patient died of respiratory failure on the 62nd hospital day. An autopsy was performed 2.5 h after death.

During the final admission, localized vesicular eruptions due to herpes zoster virus infection affected the skin of the right arm and hand. Subsequently severe hyperaesthesia and neuralgia persisted.

Results

Dermatological findings associated with DC were evident and included reticular hyperpigmentation of the skin studded with depigmented spots (Fig. 1a, b) and dystrophy of the nails (Fig. 2). Atrophy of lingual papillae was found and hypertrophic squamous epithelium with cellular atypia in the oral and anal mucosa, shown on microscopy.

An approximately 8.0-cm-sized, ill-demarcated, scirrhous carcinoma with irregular ulceration was present in the lower part of the rectum (Fig. 3a). Histologically, a poorly differentiated adenocarcinoma of the signet ring type infiltrated diffusely into the entire wall of the rectum and involved the neighbouring tissues, including the urinary bladder and the prostate (Fig. 3b). There were no metastasis to the liver, lungs or para-aortic lymph nodes; pararectal regional lymph nodes were infiltrated. Peritoneal dissemination was not found.

The voluminous, airless lungs weighed 1200 g (R) and 1000 g (L), respectively. The cut surfaces showed pale-grey, firm consolidation throughout both lungs (Fig. 4a). Histologically, the alveolar spaces were filled with eosinophilic "honey-comb" material containing clusters of cystic structure with tiny basophilic dots. There were numerous spherical or crescentic cysts identified by Grocott's methenamine silver staining (Fig. 4b).

The liver showed no evidence of cirrhosis and weighed 1560 g. There was a subtle abnormality in lobular architecture reflected by irregular distribution of central veins and crowding of portal tracts. Dilated, thin-walled, aberrant vascular channels were frequently observed in non-sclerotic portal tracts (Fig. 5a). The portal areas were free of any appreciable inflammatory infil-

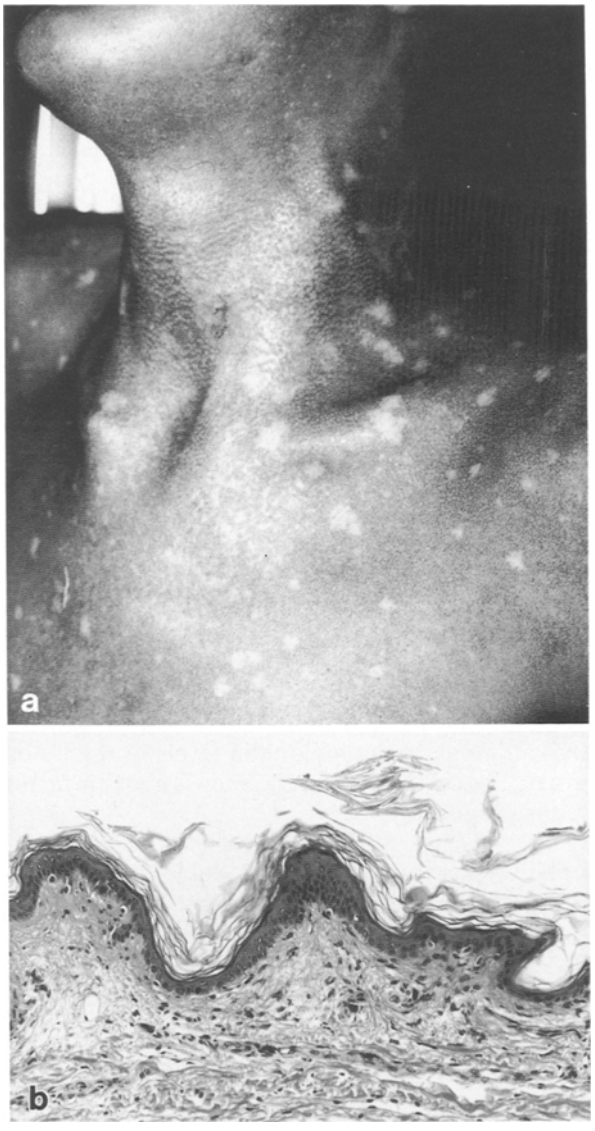

Fig. 1. a Reticular hyperpigmentation studded with depigmented spots on the chest and the neck. **b** Histologically, the epidermis is thin and wavy with loose-meshed keratinization and flattening rete ridges. Note numerous melanophages in the dermal papillae. H & E, × 50

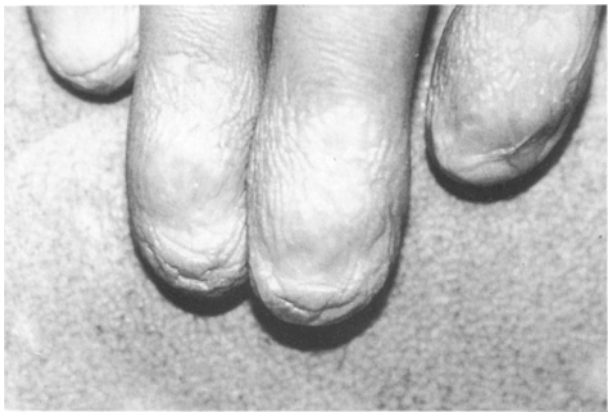

Fig. 2. Absence of finger nails

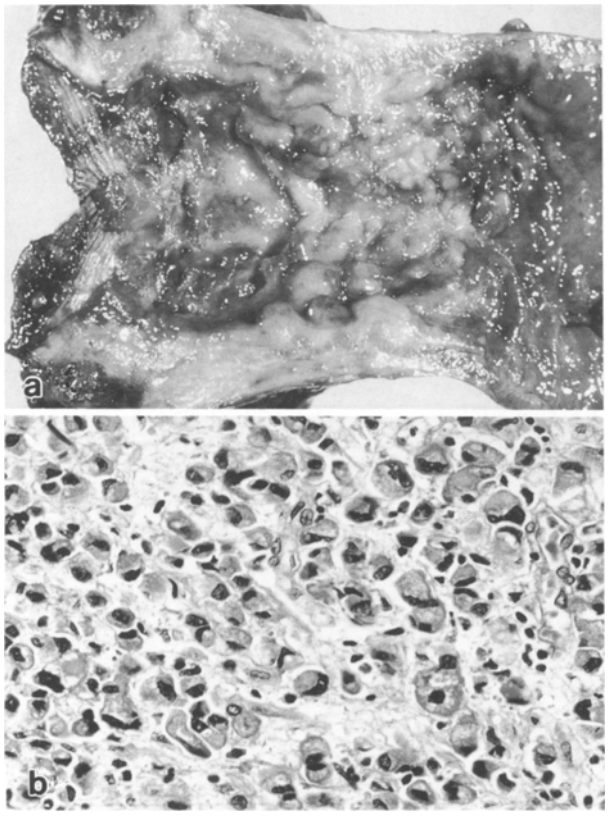

Fig. 3. a A circumferential infiltrating scirrhous carcinoma, about 8 cm in size, in the lower part of the rectum. **b** Poorly differentiated adenocarcinoma composed of signet ring cells. H & E, ×132

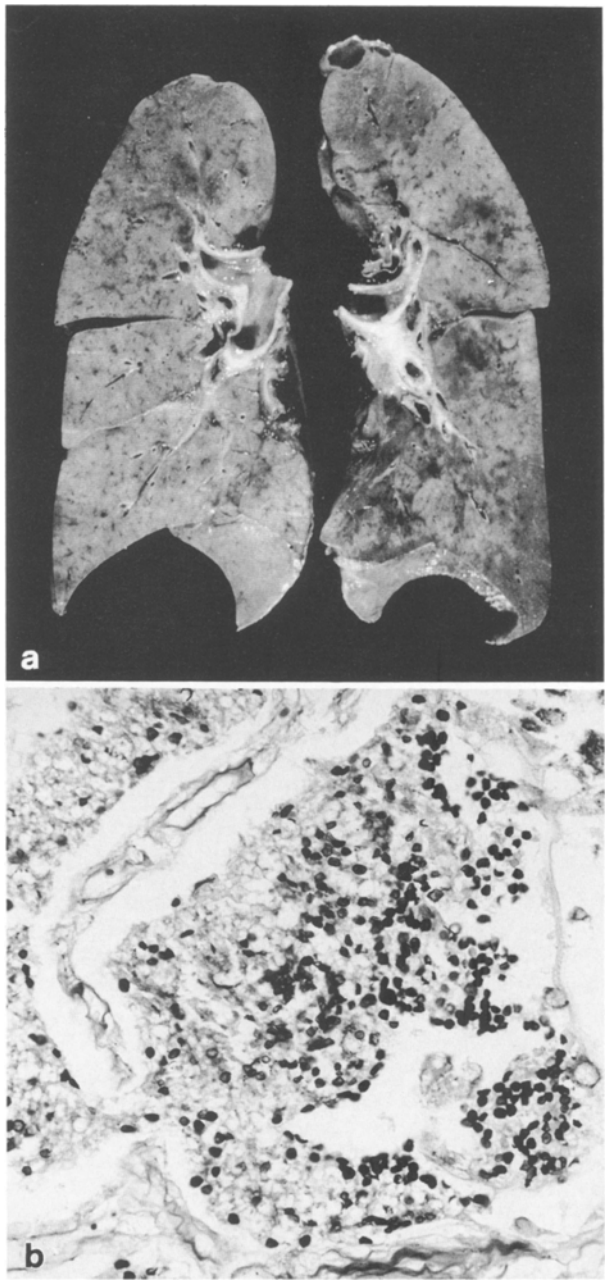

Fig. 4. a Cut surfaces of both lungs showing pale-gray, firm consolidation replacing most of the pulmonary parenchyma. **b** Spherical or crescentic cysts of *Pneumocystis carinii* in exudate. Grocott's methenamine silver, ×100

trate and sometimes contained obliterated or sclerotic portal veins (Fig. 5b). No piecemeal confluent necrosis, supporting a diagnosis of chronic hepatitis, was found.

The spleen was moderately enlarged (450 g). Histological examination showed changes of fibrocongestive splenomegaly. The sinuses in red pulp were dilated, with thickened walls; the increase in the wall thickness was due to diffuse fibrosis and an increased number of fibroblasts and macrophages in cords of Billroth. Many siderotic nodules (Gamna-Gandy bodies) were present in a perifollicular distribution.

Mild oesophageal varices were present at the lower part of the oesophagus. Other findings included aspermatogenesis in markedly atrophic testes, a normocellular bone marrow with erythroid hyperplasia, extremely slender folia of the cerebellum with a decreased cell number in the granular cell layers (Fig. 6) and atrophy of the frontal lobes of the brain (weight 1100 g), marked lymphocyte depletion and atrophy of lymphoid parenchyma in systemic lymph nodes, tonsils, gastrointestinal tract, spleen, and thymus (Fig. 7a–c), focal necrosis at the right cornu posterius and radix dorsalis in the cervical spinal cord, and a weight of only 53.5 kg for a height of 172 cm.

Fig. 5. a Several cut surfaces of dilated thin-walled aberrant vascular channels in non-sclerotic portal tract. Victoria blue, ×15. **b** Mild widening of portal tracts with obliterated or sclerotic portal veins and thin bridging fibrosis. Elastica van Gieson, ×50

Discussion

DC was first described in 1906 by Zinsser, who reported two brothers with mucocutaneous disorders consisting of "atrophia cutis reticularis cum pigmentatione, leukoplakia oris, and dystrophia unguium". The condition was documented by Engman in 1926, and later designated as DC by Cole et al. in 1930, so that it is sometimes referred to as "Zinsser-Cole-Engman syndrome". Since then more than 100 cases have been reported to date, mostly in the dermatological literature (Davidson and Connor 1988). So far as we are able to establish, autopsy findings have been briefly documented in nine cases; however, detailed histopathological information is scanty (Cole et al. 1957; Garb 1958; Bryan et al. 1965; Inoue et al. 1973; Sirinavin et al. 1975; Trowbridge et al. 1977; Mills et al. 1979; Womer et al. 1983; Wiedemann et al. 1984). The aetiology and pathogenesis remain unclear, although cytogenetic abnormalities including chromosomal breakages, gaps, or pulverizations, and DNA repair deficiency have been noted (Aguilar-Martinez et al. 1988).

The clinical features of DC have been divided into major and minor manifestations. The three major manifestations include (1) reticular pigmentation of the skin associated with dyskeratosis; (2) leucoplakia of the oral and genital mucosa; (3) dystrophy of the nails.

Additionally, various minor abnormalities of the eyes, ears, teeth, oesophagus, bone, genitourinary tract, or central nervous system have been noted less frequently (Costello 1955; Garb 1958; Milgrom et al. 1964; Womer et al. 1983; Pai and Whetsell 1989). The disease occurs almost exclusively in males and is generally thought to be transmitted as an X-linked recessive trait (Gutman et al. 1978; Connor and Teague 1981; Connor et al. 1986; Davidson and Connor 1988). However, peri-

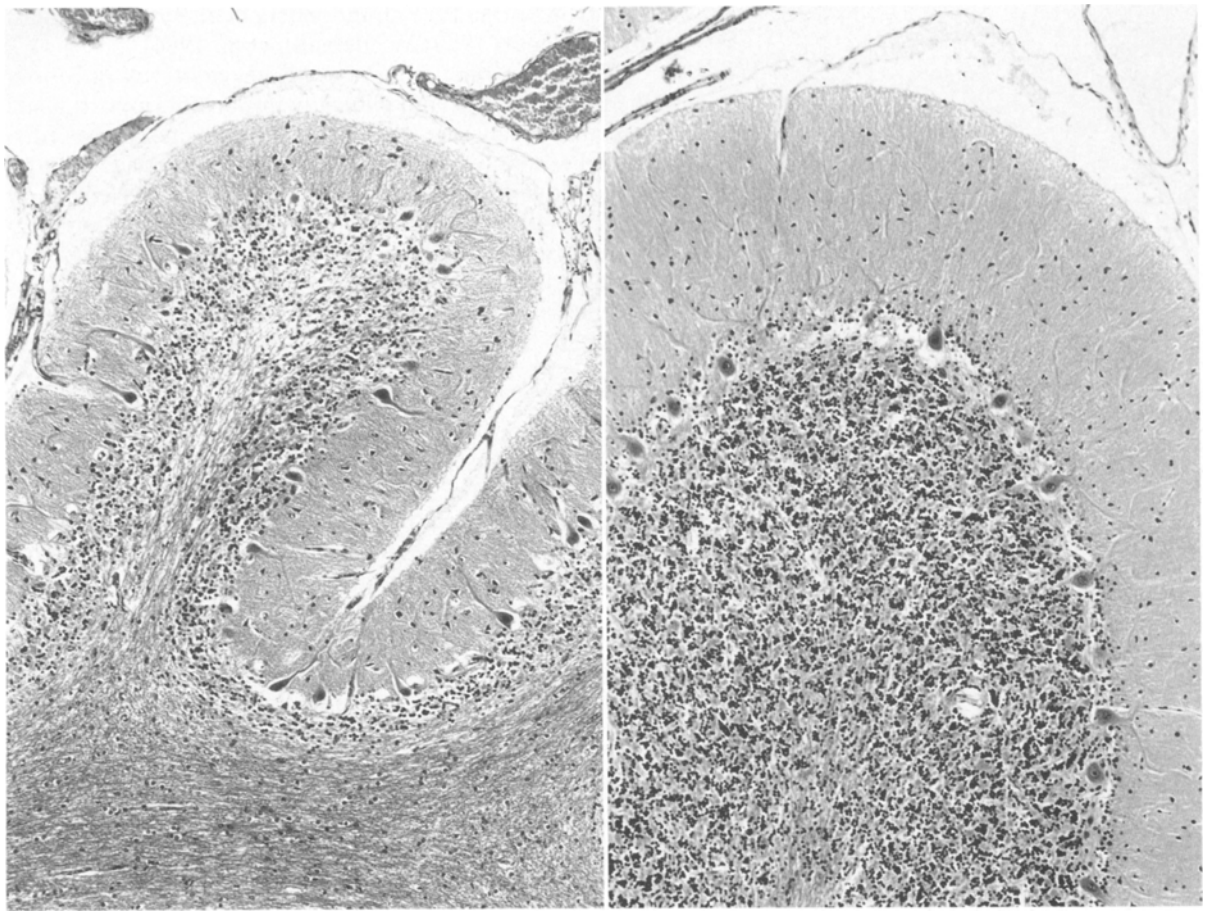

Fig. 6. Markedly slender folia of the cerebellum (*left*), compared with that of normal person (*right*). Note a decreased cell number particularly in granular cell layers. H & E, ×20

odic reports of its occurrence in females and of an autosomal recessive transmission have suggested aetiological heterogeneity (Sorrow and Hitch 1963; Georgouras 1965; Ling et al. 1985; Juneja et al. 1987; Davidson and Connor 1988). Most patients die in their teens, twenties, or thirties; most deaths occur following progressive bone marrow involvement with pancytopenia or malignancy.

In this paper we have presented histopathological features of an autopsy case with DC in a man aged 24 years. In addition to the classical dermatological pictures, there were several notable and unusual findings associated with DC. These included hepatic abnormality, histologically manifest as a non-cirrhotic portal hypertension (NCPH), signet ring carcinoma of the rectum, and atrophy of the frontal lobes and extremely slender cerebellar folia.

In the literature, several cases have been reported as having "hepatic cirrhosis", "portal hypertension" or "portal fibrosis of the liver" (Garb 1958; Bryan and Nixon 1965; Steier et al. 1972; Womer et al. 1983), but the morphological features or its pathogenesis have not been fully discussed. This is the first report describing the histopathological pictures of NCPH associated with DC. We suggest that NCPH plays an important role in the development of the splenomegaly and pancytopenia.

However, it cannot be determined whether NCPH developed incidentally or specifically in DC, but one possibility is that there are many common aetiological factors in the development of DC and NCPH.

With regard to malignant neoplasms associated with DC, it is noted that a total of 12% of patients had developed one or more tumours at the time of reporting (Davidson and Connor 1988). These have mainly occurred on mucosal surfaces showing leucoplakia and have included carcinoma of the mouth, tongue, nasopharynx, oesophagus, anus, uterine cervix and rectum (Costello 1955; Cole 1957; Sorrow and Hitch 1963; Sirinavin and Trowbridge 1975; Davidson and Connor 1988). Furthermore, rare neoplasms, for example pancreatic carcinoma, gastric carcinoma and Hodgkin's disease, have been noted (Connor and Teague 1981; Jacobs et al. 1983).

To our knowledge there have been three cases (including the present case) who have suffered from rectal adenocarcinoma (Cole et al. 1957; Garb 1958). A prominent feature is that two of the three cases had a signet ring carcinoma, which is generally considered to be a rare subtype among rectal adenocarcinoma.

Immune system abnormalities are not classically included as a part of the disease complex, but recently several reports have suggested that primary immune defect is a serious complication in this disorder (Sirinavin

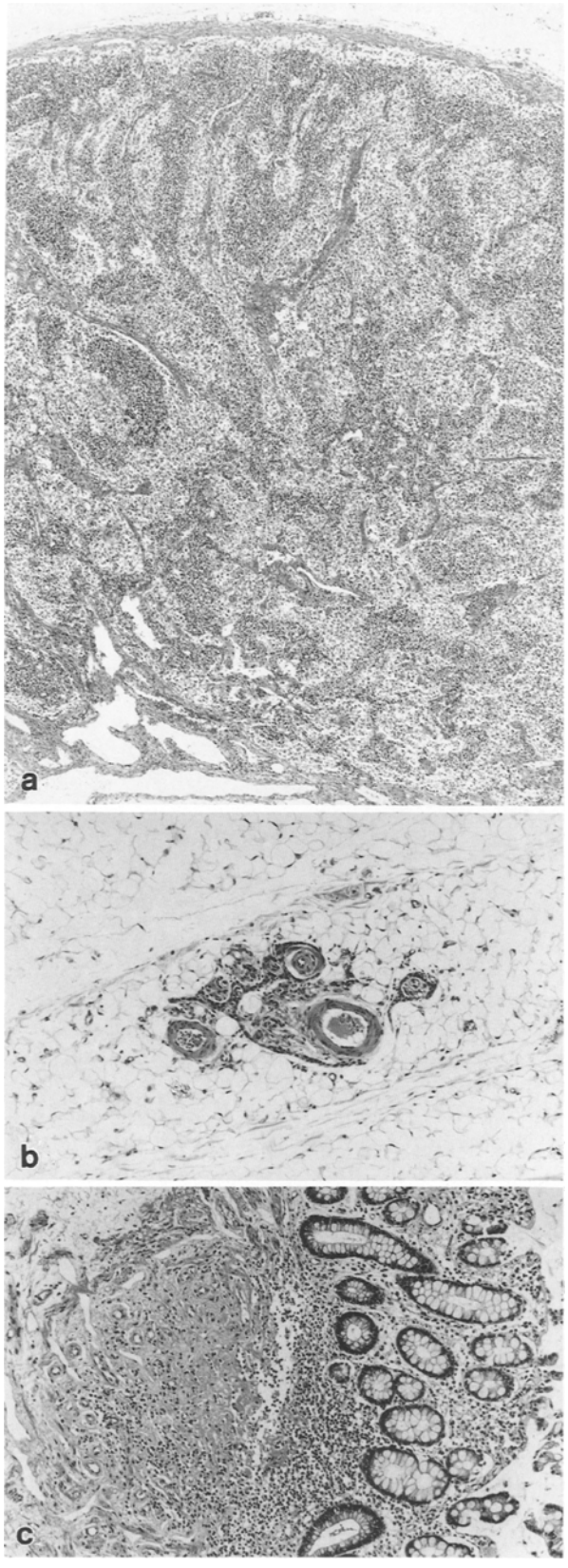

Fig. 7. **a** Low-power view of cervical lymph node showing marked lymphocyte depletion, lack of lymph follicles and dilated sinuses. H & E, ×10. **b** Marked involution of the thymus with prominent lymphocyte depletion. H & E, ×33. **c** Atrophic lymph follicle with hyalinization in the colonic mucosa. H & E, ×33

and Trowbridge 1975; Fundenberg et al. 1979; Giannetti and Seidenari 1980; Wiedemann et al. 1984).

P. carinii pneumonia or cytomegalovirus infection, the most frequent and clinically important opportunistic infection occurring in immunocompromised patients, have been noted in recent publications (Sirinavin and Trowbridge 1975; Trowbridge et al. 1977; Wiedemann et al. 1984). Abnormalities of cell-mediated and humoral immunity have been reported in patients with DC, but these changes have been inconsistent, and their pathogenetic roles are undefined (Fundenberg et al. 1979; Giannetti and Seidenari 1980; Colvin et al. 1984; Wiedemann et al. 1984).

In 1973, Inoue et al. first described the histological findings in the lymphoid system as follows: the thymus was a fatty mass and no normal thymic tissue could be found while the spleen and lymph nodes were severely depleted with some fibrosis. Subsequently, Trowbridge et al. (1977) and Wiedemann et al. (1984) have also noted thymic aplasia and lymphocyte depletion of the spleen and lymph nodes. In our case, similarly, marked lymphocyte depletion with a paucity of lymph follicles and atrophy of lymphoid parenchyma were observed in systemic lymph nodes, spleen, tonsils, gastrointestinal tract, and thymus. These alterations show no specific involution differing from that seen in the lymphoid system in other conditions, such as the end phase of AIDS or the late stage of long-term administration of anti-cancer agents. However, considering the normal levels of serum immunoglobulins with the morphological features, there is evidence to support a defect in the cell-mediated immune system in patients with DC. Although the pathogenetic nature of the immunodeficiency remains unclear, the immune defect is a major life-threatening component of DC.

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