Virchows Arch. A Path. Anat. and Histol. 378, 329–340 (1978)

Virchows Archiv A

Combined Immune Deficiency Syndromes with Primary T-Cell Defect and Partial B-Cell Reactive Hyperactivity* **

Immunological and Morphological Analysis of Two Unusual Cases

G.G. Konorza, G.R.F. Krueger, and K.G. Evers

Immunopathology Laboratories, Pathology Institute, University of Cologne (Dir. Prof. Dr. R. Fischer)
and Children's Clinic, City of Cologne (Dir. Prof. Dr. H. Ewerbeck)

Summary. Two cases of combined immunodeficiency with lymphopenia, thymic dysplasia, and defective immunoglobulin production are reported. Both show selective hypo-gammaglobulinemia (IgG and IgA respectively) and selective hyper-gammaglobulinemia (both IgE, IgA, and IgM respectively). The cases are classified, by correlation of clinical and histopathological data as a variant of Fireman's disease.

Key words: Immune deficiency disease – Fireman's disease – Pathology – Clinical course.

Zusammenfassung. Es werden zwei Fälle von kombiniertem Immunmangelsyndrom beschrieben mit Lymphopenie, Thymusdysplasie and fehlerhafter Immunglobulinbildung. Beide zeigen eine selektive Hypo-Gammaglobulinämie (IgG bzw. IgA) und selektive Hyper-Gammaglobulinämie (beide IgE, IgA bzw. IgM). Die Klassifikation erfolgt durch eingehende Korrelation klinischer und pathologisch-anatomischer Daten als Variante der Firemanschen Erkrankungen.

Introduction

The number of clearly defined immunodeficiency syndromes is rising as immunological methods gain widespread clinical use. The diseases are classified clinically, as pathological examination can, as yet, demonstrate general reaction patterns only. However, little pictorial material of the histology of clinically

* Immunopathology Studies were done with the help of grant Kr 476/3-4 of the German Science Foundation

** We wish to thank Miss B. Koch for technical assistance and Mr. R. Grossmann for photography

Address offprint requests to: Prof. Dr. G. Krueger, Pathology Institute, University of Cologne, Joseph-Stelzmann Str. 9, D-5000 Cologne 41, Federal Republic of Germany

0340-1227/78/0378/0329/$02.40

defined cases has been published (Heymer et al., 1977). We therefore wish to present two similar cases of combined immune deficiency syndromes and attempt to classify them amongst the syndromes already published.

Case Material

Case 1 (J.B.)

a) History and Clinical Course (see Table 1). This 10 month old baby boy has a striking family history of immune deficiency diseases affecting four males on the maternal side of his family, leading to death in early childhood in each case. The patient was under medical supervision from birth.

Hypo-gammaglobulinemia (IgM, IgG, IgD) with normal or slightly elevated IgE was found. A negative delayed-type skin reaction to sensitization with streptokinase-streptodornase (SK-SD), tetanus toxoid, and pneumococcal polysaccharide was obtained and mixed lymphocyte culture was non stimulatory. X-ray failed to show a thymus shadow. Peripheral lymphocyte counts were normal, but the cells failed to be stimulated by phytohaemagglutinin (PHA).

Clinically the child was unremarkable until, at the age of five months, a series of recurring infections occurred, rhinitis, pharyngitis, and bronchitis. These responded well to antibiotic therapy initially (ampicillin and erythromycin). When he was eight months old, his mother developed an influenza-like infection, and a week later the child was hospitalized because of a temperature of 39.5° C, coughing, tachypnoea, irritability, and restlessness. Skin and visible mucosae were palely cyanotic. The white blood count (WBC) showed 15,200 leukocytes/cu mm with 84% neutrophils and 13% lymphocytes. Chest-X-ray showed bilateral diffuse pneumonic infiltrates with alveolar components reminiscent of a Pneumocystis carinii infection (no organisms were demonstrated).

Immediate therapy consisted in placing the child in an oxygen tent, intravenous fluid replacement, and antibiotics (kanamycin, colistin sulfate, cephalotin, and pentamidine), further gammaglobulin (4 times 2 ml i.m. within 12 h). After 3 days, temperature and chest-X-rays were normal and kanamycin, colistin, and cephalotin were discontinued. However, further bouts of pneumonia recurred with WBCs between 7400 and 47,000/cu mm and up to 95% neutrophils with absolute lymphocytopenia.

Further treatment was symptomatic, as above. Later, severe diarrhoea resulted in salt-losing and protein deficiency syndromes. Repeated immune studies showed negative skin reactions to diphtheria toxin, tetanus toxoid, SK-SD, trichophytin, monilia, and mumps. No sensitization to DNCB (dinitrochlorobenzene) was achieved.

One month after onset of his illness, aspergillus flavus was cultured from the stool and candida parapsilosis from the blood. Treatment with amphotericin B was started. On the 45th day, grossly bloody stools were noticed, and the patient died one day later with severe cardiac arrhythmias.

The final clinical diagnoses were:

1) Combined X-linked inherited immune deficiency syndrome
2) *Aspergillus flavus* pneumonia
3) Thrombocytopenia and erythropoietic hyperplasia
4) Gastro-intestinal hemorrhage
5) Uraemia

Table 1. Serum immunoglobulins in our patients (mg/100 ml)

	IgG	IgM	IgA	IgE	IgD
Case 1	370	90	1200	152	0
Case 2	500	900	7	380	nd
Normal	800–1.800	30–280	80–400	100	300

nd: not done

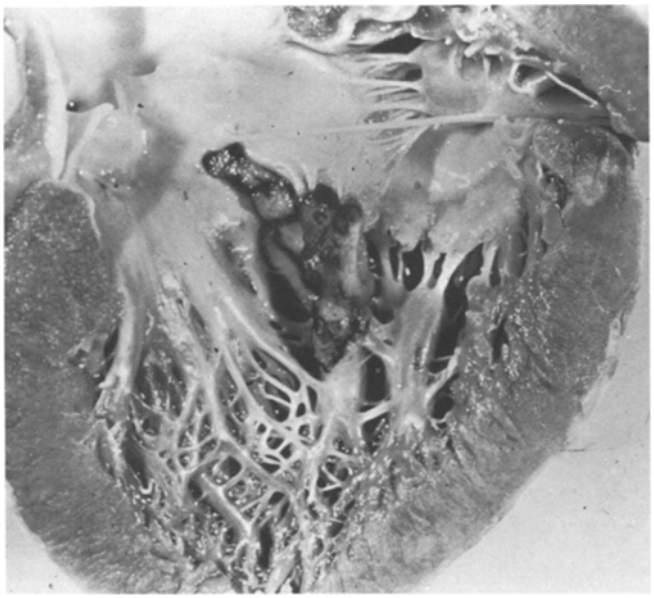


Fig. 1. Mycotic endocarditis with fungal thrombus (Patient 1)

b) Autopsy Findings. The autopsy of the 10 months old, 5 kg baby revealed generalized aspergillosis with multiple fungal abscesses in trechea, heart, lungs, and kidneys. The heart valves were partly covered by mycotic thrombi (Fig. 1). One pulmonary fungal abscess had ruptured into the pleural cavity causing pneumothorax. The entire lymphoreticular system was distinctly hypoplastic, the thymus weighing only 2.5 g instead of the normal 30 g. Histologically, the thymus was cystic with scattered diffuse and nodular lymphocytic aggregates. There was no clear separation into cortex and medulla (Fig. 2). Thymic epithelium and Hassall's corpuscles where wholly absent. The lymph nodes showed a loose fibro-reticular stroma with few accumulations of lymphoid cells and fibro-histiocytic cells in the pre-existent cortex. The peripheral sinuses appeared dilated and empty, whereas the intermediary sinuses were collapsed. Very few sinus histiocytes were visible (Fig. 3).

The spleen consisted of a loose fibro-reticular stroma with dilated sinusoids and occasional small lymphocytic foci at the site of pre-existent follicles (Fig. 4). As in the thymus and lymph nodes, the cells were medium sized, of lymphoid type with coarsley granular nuclei.

The tonsils and Peyer's patches were diffusely atrophic as was the lymphatic apparatus of the appendix. The bone marrow displayed diffuse lymphocytosis with maturation arrest of the red and white precursors. Further findings were diffuse fatty degeneration of th liver and extensive tubular necroses in both kidneys; cystic change in the pancreatic acini as seen in uremia was also noted. The intestines showed a marked reduction of lymphocytes and plasma cells in the lamina propria and diffuse atrophy of the mucosa (Fig. 5). A fresh

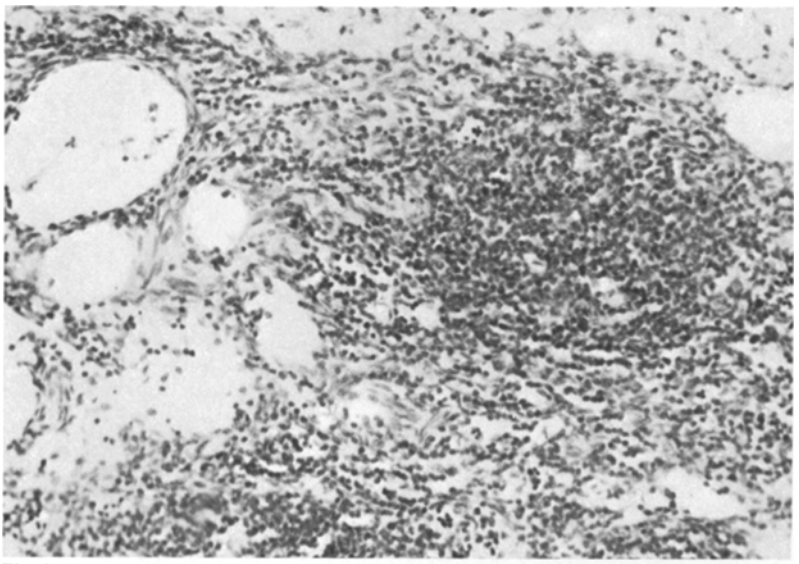


Fig. 2. Severe thymic dysplasia with cyst formation and absence of epithelial elements (Patient 1; H & E, ×150)

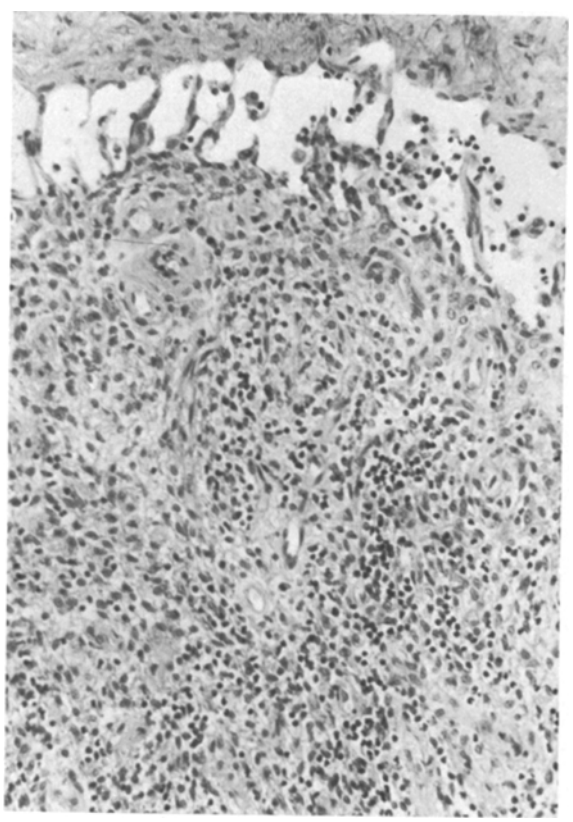
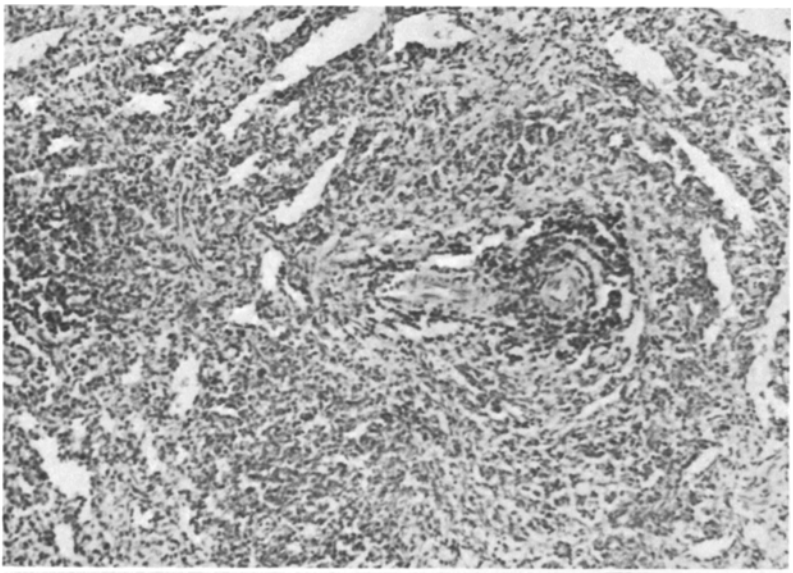


Fig. 3. Severe diffuse atrophy of lymph node, cortex and paracortex (Patient 1; H & E, ×375)



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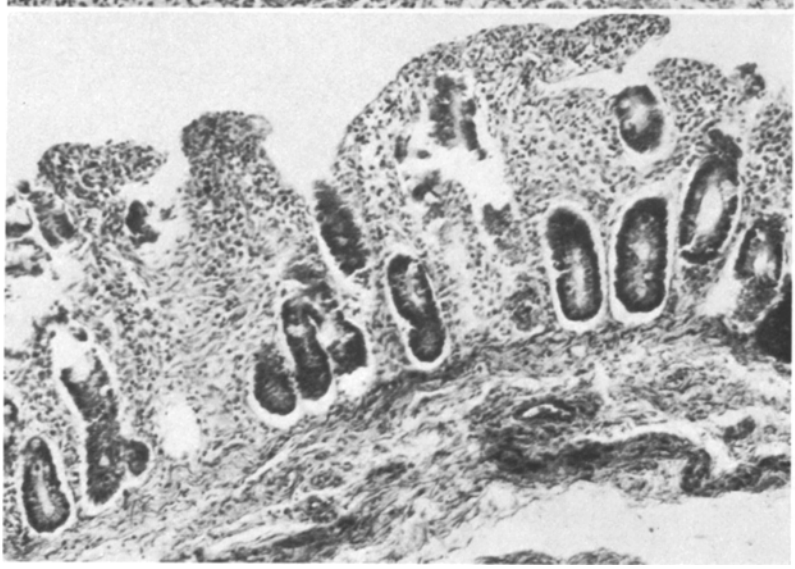

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Fig. 4. Severe diffuse atrophy of the spleen with only small follicular remnants (Patient 1; H&E, ×150)

Fig. 5. Moderate diffuse atrophy of small intestine with shortening of villi, reduced lympho-plasmacellular population of lamina propria, crypt degeneration (Patient 1; H & E, ×150)

duodenal ulcer had caused massive gastro-intestinal hemorrhage, the ultimate cause of death.

The final pathologic diagnoses were:

1) Thymic dysplasia with generalized lymphoreticular hypoplasia
2) Generalized septic aspergillosis with

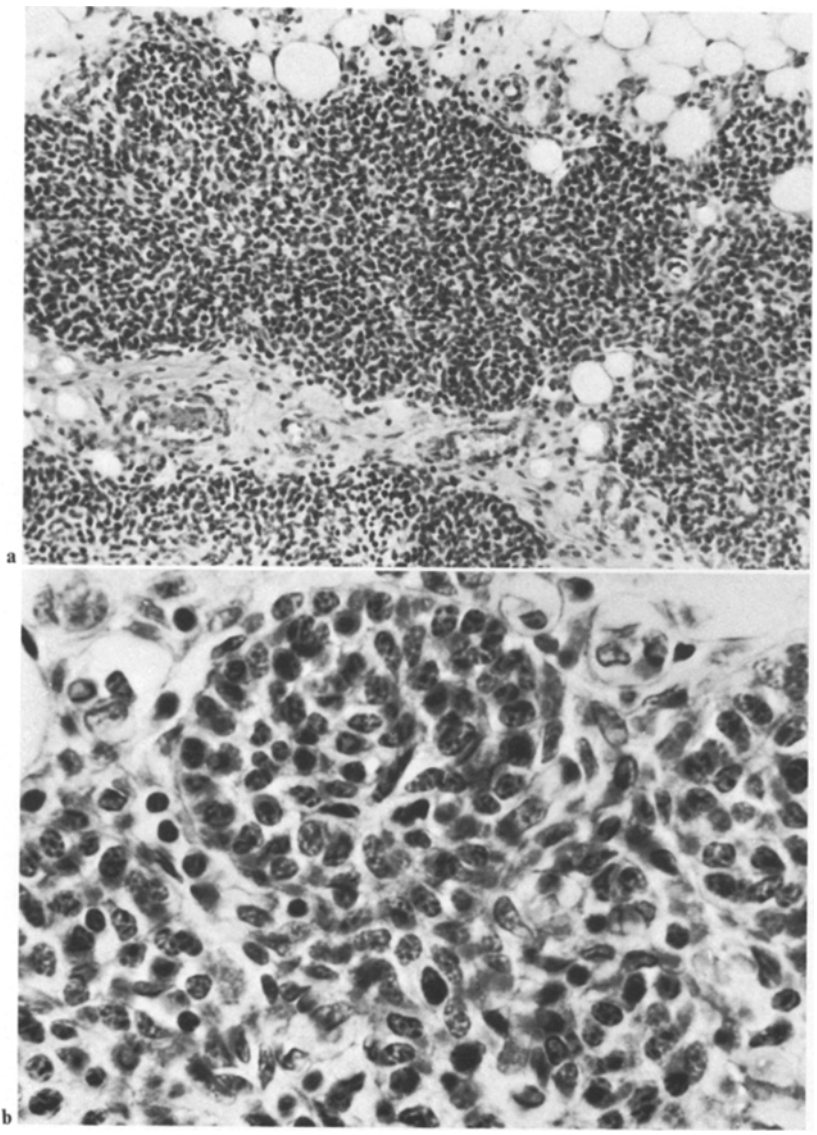

Fig. 6a and b. Severe thymic dysplasia with absence of epithelial elements and diffuse fibroreticular stroma with scattered unclassified lymphoid cells (Patient 2). H & E, **a)** ×150; **b)** ×600

3) Fungal endo- and myocarditis and fungal pneumonia, with pneumothorax secondary to rupture of fungal abscess

4) Fatal gastro-intestinal hemorrhage from duodenal ulcer.

Case 2 (S.S.)

a) History and Clinical Course (see Table 1). The patient was the only child of healthy parents; a careful family history showed no indication of immunodeficiency diseases in any member.

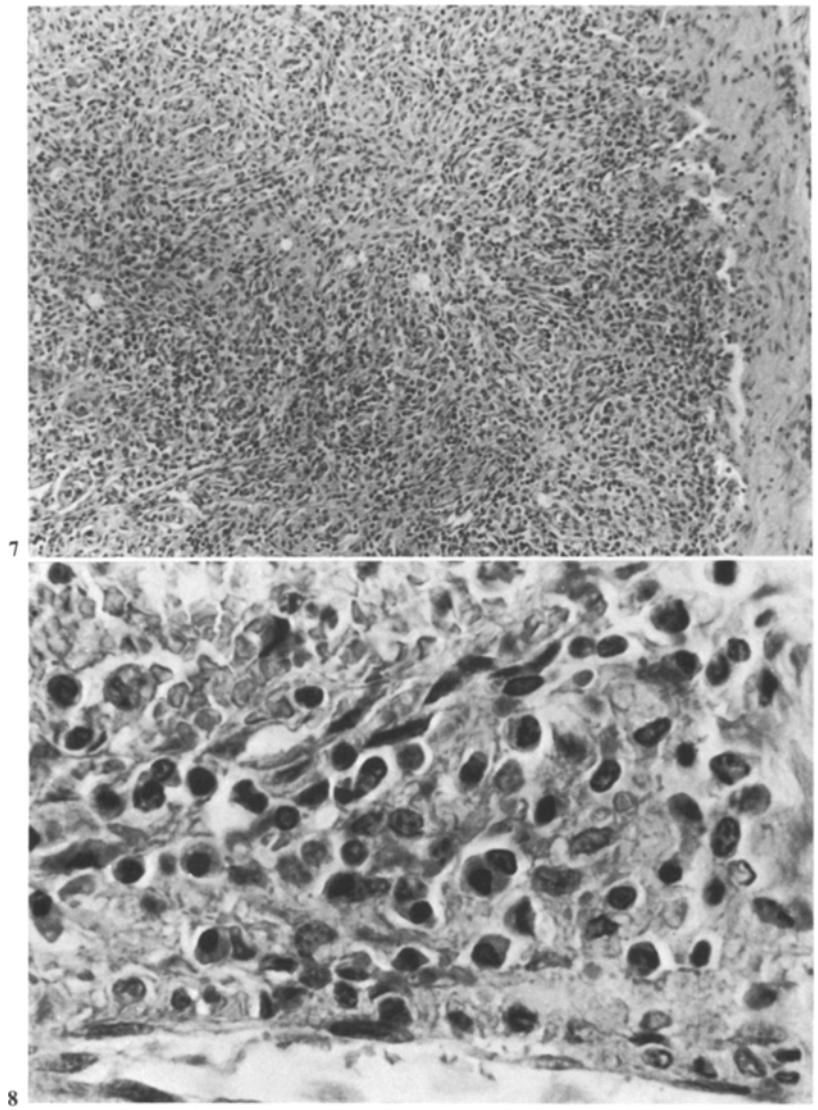

Fig. 7. Severe diffuse atrophy of lymph node (Patient 2; H & E, ×150)

Fig. 8. Scattered plasma cells in atrophic lymph node (Patient 2; H & E, ×600)

This female child was born at term and developed normally until the age of three months when she was admitted to the hospital with seborrhoic dermatitis, erythrodermia, and purulent otitis media. The patient responded well to antibiotic treatment and was discharged. One month later, following BCG inoculation, she was again admitted because of a generalized vesicular rash affecting the whole integument. (The BCG vaccine was later shown to be highly virulent (Helwig, 1976).) She was running a high temperature and had generalized lymphadenopathy. A lymph node biopsy taken at this time revealed absence of germinal centers, extreme scarcity of lymphocytes in the T-cell region (paracortex) with pronounced proliferation of poorly classifiable reticularhistiocytic cells.

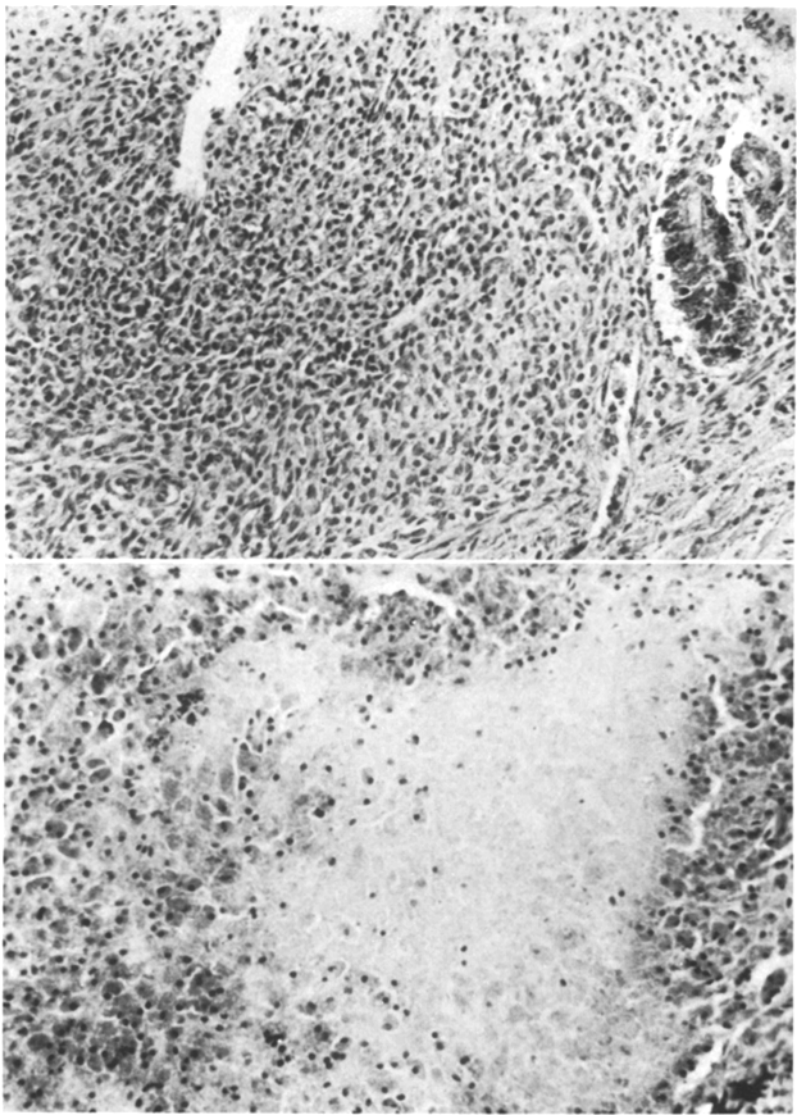

Fig. 9. Severe atrophy of Peyer's patch (Patient 2; H & E, ×150)

Fig. 10. Necrotizing granuloma at BCG inoculation site (Patient 2; H & E, ×150)

The clinical course was further characterized by recurring pyodermia, pneumonia, and finally purulent meningitis. *B. proteus* was cultivated from liquor. Erythrodermia with rough flaking of skin developed 10–14 days after transfusion of washed red blood cells for anemia.

Immunological findings (Table 1) revealed an extreme lack of IgA (7 mg%), IgE and IgM were distinctly elevated. There was an obvious eosinophilia of 10%. Complement factors C1 to C5 were found to be normal. Intradermal tests revealed no reactions to tuberculin, candida antigen, SK-SD, or DNCB after sensitization. The nitroblue tetrazolium test (NBT-test) for granulocyte function was normal. Chest-X-ray showed to thymus shadow. In spite of antibiotic therapy (tetracycline, carbenicillin, cloxacillin, aminoglycosides) the patient died of rapidly progressing meningitis.

The final clinical diagnoses were:

1) Combined immune deficiency (T-cell deficiency and B-cell deficiency of IgA type)
2) Recurrent bacterial pneumonia
3) *B. proteus* meningitis.

b) Autopsy Findings. At autopsy we found histological alterations compatible with the clinical diagnosis of combined immune deficiency. Severe thymic hypoplasia (weight 0.9 g) with corresponding hypoplasia of the T-cell regions in the lymphoreticular tissues was seen. The thymic hypoplasia was particularly distinguished by the absence of Hassall's corpuscles (Figs. 6 and 7). The abnormal appearance of the B-cell regions was apprently due to atrophy, i.e. secondary involution after formation of a normal anlage. These secondary changes were most probably due to severe and repeated infections, representing an exhaustion phenomenon. This finding was emphasized by the large numbers of regressing or hyalinized germinal centers in lymph nodes and spleen. The clinically diagnosed hyper-IgM and IgE globulinemia correlated well with moderate diffuse plasmacytosis of the otherwise atrophic lymphatic organs (Fig. 8), and may also have been induced by repeated infections. The lamina propria of the gastrointestinal tract, however, was grossly deficient in lymphocytes and plasma cells, and by fluorescence microscopy IgA and IgM producing cells were not identified. There was a moderate villous atrophy of the intestinal mucosa and a striking atrophy of Peyer's patches (Fig. 9). These alterations have been observed in immunodeficiency with recurrent infections.

At the site of the BCG inoculation an extensive necrotizing granuloma was found with macrophages, scattered plasma cells, and abundant acid-fast bacteria (Fig. 10). No characteristic epithelioid cells or Langhans cells were identified. In the adjacent soft tissue there was extensive scarring.

The final pathologic diagnoses were:

1) Thymic dysplasia with generalized dysplasia of thymus-dependent regions and atrophy of B-cell regions
2) Generalized fungal dermatitis (candida)
3) Extensive bacterial pneumonia and bacterial meningitis (*B. proteus*)
4) Septic shock.

Discussion

In both cases, histopathological investigations alone did not provide sufficient data to classify the immunodeficiency syndromes described. However, the following statements were permissible:

A diagnosis of primary thymic hypoplasia was possible due to the rudimentary differentiation of cortex and medulla with absence of epithelial elements, especially of Hassall's corpuscles; in secondary atrophy Hassall's corpuscles are present and tend to be increased in number. The lymphocytopenia of thymus-dependent regions of the lymphoreticular tissues was a consequence of the primary thymic dyplasia. Both findings correlated well with the clinically demonstrated defective cell-mediated immunity. In the first case this was shown before

repeated severe infections could have caused secondary immunodeficiency. A clinico-pathologic diagnosis of T-cell immunodeficiency with thymic dysplasia should be made (apparently X-linked inherited in the first case).

In this context it is interesting that BCG inoculation in the second case was not followed by the characteristic epithelioid granuloma formation. The atypical necrotizing granulomata observed in this case may possibly have been a consequence of deficient T-cell function.

In addition, both cases showed distinct atrophy of thymus-independent regions of lymphoreticular tissues such as lymph node cortex and medullary cords, the intermediate follicular zone of the spleen, and the follicular parts of the tonsils and Peyer's patches. This suggested a concomitant humoral immunodeficiency. The findings in one case, exhibiting atrophic germinal centers suggest secondary (post-infection) atrophy, but in the other it was difficult to decide, on morphological grounds alone, whether one was dealing with primary B-zone dysplasia or with atrophy secondary to repeated severe infections. Additional clinical and immunological examinations permitted further differentiation.

Before significant infection occured in case 1, it had been shown that IgG levels were depressed (IgA was depressed in case 2 immediately after admission to the hospital), and IgM levels slightly below normal. In both cases, therefore, there must have been an antecedent selective hypofunction of the humoral immune system, which would imply that the morphological alterations observed must have been, at least in part, due to primary dysplasia. This hypoplasia was probably restricted to certain cell classes (and therefore represented dysplasia rather than hypoplasia of the B-cell system) as evinced by the normal or even increased amounts of other immunoglobulins. Immunopathologically, such a diagnosis may only be made by immunocytological T- and B-cell determinations in suspensions of living cells from lymph node biopsies.

IgE was elevated in both cases, while IgM was distinctly raised in case 1 and IgA in case 2. It must therefore be assumed that the appropriate immunoglobulin secreting tissues were intact. Among these is the disseminated lymphoreticular apparatus of the gastro-intestinal and the respiratory mucosa, which at autopsy was also depleted of lymphocytes and plasma cells. This again suggests secondary atrophy following repeated infections rather than primary hypo- or dysplasia.

In conclusion, combined clinico-pathologic data suggest the following diagnosis: Lymphopenic thymic dysplasia with T-cell and selective B-cell immunodeficiency and selective B-cell hyperactivity (probably of the secretory immune globulin system); X-linked recessive in case 1. Neither pathological nor clinical evidence was available as to whether the selective hyperactivity of the B-cell system was primary or secondary.

The syndromes described in this report should be classified in the presently available categories of immune deficiency syndromes. Following the scheme suggested by the WHO (Kunkel et al., 1972), our two cases should probably be labeled as "variable immunodeficiency, largely unclassified". However, since other classifications are widely used we shall also compare our two cases with those. Having a combined immunodeficiency syndrome, our patients differ from

what has been described as pure B-cell or pure T-cell defect (Bruton, 1952; Nezelof et al., 1964; DiGeorge, 1968). At best, they resemble the Swiss type agammaglobulinemia, particularly the X-linked type (e.g. thymic alymphoplasia (Rosen et al., 1966; Sell, 1968)). However, the illness of one of our patients was apparently not X-linked, and the syndromes differ from Swiss type agammaglobulinemia by their selective B-cell hyperactivity. Selective B-cell deficiency, IgE hypergammaglobulinemia, thymic dysfunction, and repeated skin affections (case 2) are reminiscent of the Wiskott-Aldrich syndrome (Cooper et al., 1968; Thaler et al., 1977). This similarity is superficial, since the dermatological pathology of our patient was related to extensive fungal infection, thymic dysfunction was primary rather than secondary, B-cell deficiency was not specifically directed towards polysaccharide antigens, and primary thrombocytopenia was not present.

In 1966, Fireman and collaborators observed a case of lymphopenic immunodeficiency with low serum IgG and IgA levels and elevated serum IgM (over 200 mg%). Berg and Johannson (1967) reported a similar syndrome with thymic dysplasia, defective cell-mediated immunity, decreased serum IgG and IgA, and almost normal serum levels of IgM, the synthesis of which was probably delayed. In both cases there was selective B-cell deficiency, as in our cases. In addition, Fireman et al. observed what was assumed to be a compensatory rise in IgM, again similar to our cases. The immunoglobulin classes elevated in our two patients, however, varied (IgA and perhaps IgE in the first baby, IgM in the second) which may be a result of differing extraneous antigenic stimulation causing compensatory rise of immunoglobulins, rather than a primary hyperactivity of the respective cell classes. We suggest therefore classifying the syndromes described in our paper as variants of Fireman's disease.

A common pathogenetic mechanism cannot be suggested from the similarities noted. Whereas the abnormal immunoglobulin pattern in Fireman's disease hints at defective memory cell function (T-cell defect; undisturbed IgM primary response; suppressed IgG synthesis at second antigenic challenge), in our first case at least a primary selective B-cell defect seems more probable.

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Received February 20, 1978