Thymic Alymphoplasia, Monoclonal Gammopathy, and *Pneumocystis Carinii* Pneumonia in an Infant

D. M. O. BECROFT and R. DOUGLAS

From the Princess Mary Hospital for Children, and the Auckland Blood Transfusion Service, Auckland, New Zealand

Immunological deficiencies have been shown in many children bearing thymic malformations. In some children both cell-mediated and humoral immune reactions have been depressed, the former indicated by abnormalities of delayed hypersensitivity and of homograft rejection, and the latter by deficient antibody responses and hypo- γ -globulinaemia. Such findings are in accord with the experimental evidence that the thymus acts as a 'protagonist in the development of immunological capacity' (Holborow, 1967). Unfortunately, the inconstancy of these deficiencies in other cases has prevented a more precise definition of the role of the thymus in human immunogenesis. Not all children with congenital thymic defects have been hypo- γ -globulinaemic, though the patterns of immunoglobulin synthesis in these exceptions have varied widely and have often been abnormal.

The infant with thymic dysplasia who is the subject of this report presented a further variation in having an immunoglobulin with the restricted electrophoretic and antigenic properties characteristic of the M-type proteins found in multiple myeloma and related neoplastic diseases.

Case Report

This male infant, birthweight 2.9 kg., was delivered normally after an uneventful pregnancy. He progressed satisfactorily for 4 weeks, but then began vomiting; pyloric stenosis was suspected, and he was admitted to hospital. At 4 weeks old he weighed 3.3 kg. No abnormalities were found clinically. A barium meal showed gastro-oesophageal reflux, and with feeding in the upright position and sedation he vomited less and gained a little weight. During this admission his blood Hb and urea, serum electrolytes, calcium and phosphorus, urine analysis, and chest x-ray were normal. His white blood counts are listed in Table I.

He was readmitted aged 12 weeks because he had failed to gain weight. He then weighed 3.8 kg. He was small and thin, but there were no other clinical abnormalities. X-rays of his chest showed a minor focal accentuation of lung markings. His serum electrolytes, calcium, phosphorus, and glucose, and his blood urea were again normal. Hb 10.9 g./100 ml. There was a nasal discharge from which *Staphylococcus pyogenes* was cultured. Urine analysis was normal. He remained in hospital vomiting intermittently and having some diarrhoea, but these symptoms were never severe enough to cause dehydration. After 2 weeks a macular rash appeared on his trunk and persisted. The skin of his buttocks and ano-genital area became excoriated. He had oral moniliasis which was resistant to therapy, and it was suspected that the skin was similarly infected. He gained weight very slowly.

After 8 weeks in hospital he became dyspnoeic and cyanosed. There was clinical and radiological evidence of consolidation advancing through the lung fields. His condition deteriorated rapidly and he died at 20 weeks. Hb terminally was 12.2 g./100 ml. and the red cell morphology was normal.

Necropsy. The body was poorly nourished (weight 4.9 kg., crown-heel length 61 cm.). There was a diffuse macular rash merging into confluent, partly crusted erythema over the neck, groins, buttocks, and perineum. The lungs were uniformly firm and heavy. In all

TABLE I
White Blood Counts

Age (wk.)	Total WBC/cu.mm.	Absolute Lymphocyte Count/cu.mm.
4	7,900	790
6	5,000	1,500
12	10,400	3,800
16	9,600	3,900
20	15,800	6,800
21	23,100	4,200
21	19,300	3,900

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FIG. 1.—Thymus: the dysplastic lobules contain few lymphocytes and no Hassall's corpuscles. (H. and E. $\times 145$.)

histological sections the majority of alveolar ducts and alveoli contained a foamy exudate characteristic of *Pneumocystis carinii* infection, and typical organisms were demonstrated in smears and sections (Becroft and Costello, 1965). There was a patchy interstitial and peribronchiolar infiltration by lymphocytes and numerous pyroninophilic plasmacytes and proplasmacytes.

The thymus was a small, firm, white nodule in the superior mediastinum weighing less than 1 g. In sections the thymic lobules were well defined, but extremely small, consisting largely of epithelial thymocytes (Fig. 1). Hassall's corpuscles were absent and there were only a few small lymphocytes.

Many retro-peritoneal and mesenteric lymph nodes were enlarged to as much as 2 cm. in diameter. All nodes examined histologically lacked normal differentiation into a cortex and medulla, and consisted of a loose stromal network containing numerous reticular cells with well-defined eosinophilic cytoplasm (Fig. 2). Lymphocytes were sparse, and though some were aggregated about arterioles, there were no true primary or secondary follicles. Plasmacytes and pro-plasmacytes were abundant in all nodes (Fig. 3).

The spleen weighed 20 g. Penicilliary arteries were surrounded by fibrillary zone containing loosely arranged reticular cells, plasmacytes, and a homogeneous eosinophilic deposit which did not retain stains for amyloid (Fig. 4). These pale-staining areas had a peripheral cuff of lymphocytes varying from a few cells to well-developed lymphoid follicles without germinal centres. There were many plasmacytes in the red pulp. In the liver some portal tracts contained small aggregations of lymphocytes, reticular cells, and many plasmacytes. On

macroscopic inspection no tonsillar tissue was apparent and the appendix was normal, but no sections were available from these organs. No submucosal lymphoid tissue was detected in serial sections of the small and large intestines. The lamina propria of the intestines was poorly cellular, but did contain scattered plasmacytes and lymphocytes. The bone-marrow had normal cellularity. Some lymphocytes and plasmacytes were identified, but in sections were difficult to distinguish from other marrow elements. No abnormalities were detected in other organs.

Serum Immunoglobulins

Hyper- γ -globulinaemia was first demonstrated by paper electrophoresis of serum when the patient was 12 weeks old, but the presence of a discretely migrating component was overlooked at the time (Fig. 5a). Total serum proteins were then 6.6 g./100 ml., and the serum γ -globulin level (by elution) was 1.3 g./100 ml. All other investigations were performed on serum obtained *post mortem*; the validity of such specimens for protein studies has been confirmed by Martinez-Tello and Braun (1965). Total serum proteins were 6.6 g./100 ml. By photometric scanning after electrophoresis on cellulose acetate the serum albumin was estimated as 2.9 g./100 ml., and serum γ -globulin as 2.0 g./100 ml. Immunoassays of immunoglobulin fractions (performed in the laboratory of Dr. David Gitlin by methods similar to those described by Fireman, Johnson, and Gitlin, 1966): IgG 1800 mg./100 ml.; IgA 180 mg./100 ml.; and IgM approximately twice the normal adult level. An independent immunoassay (by Dr. John Scott using the method of Soothill, 1962) gave an even

FIG. 2.—Lymph node: subcapsular region showing severe depletion of lymphocytes and hyperplasia of reticular cells. (H. and E. $\times 145$.)

higher IgG level of 2400 mg./100 ml. (± 400 mg./100 ml.).

Discrete electrophoretic migration of a large slow-moving fraction of the γ -globulin was noted on cellulose

acetate and was particularly striking on starch gel. On the latter, one major band characteristic of an M-component and at least one minor band were apparent (Fig. 5b). Immunoelectrophoresis revealed IgA and IgM to

FIG. 3.—Lymph node: higher magnification than Fig. 2, showing numerous plasmacytes and proplasmacytes. (H. and E. $\times 640$.)

FIG. 4.—Spleen: lymphoid follicle having a central pale area containing plasma cells and a proteinaceous deposit, but no germinal centre. (H. and E. $\times 145$.)

be present in amounts consistent with the above quantitative estimations. The precipitin arcs of these fractions had normal configuration, whereas the IgG arc was distorted, with bowing towards the antibody reservoir in the slow-moving region consistent with the presence of the discretely migrating abnormal component (Fig. 5c). The presence of both K and L antigens in the unfractionated serum was confirmed using an Ouchterlony plate technique and antisera to κ and λ light polypeptide chains (Hyland Laboratories). Relative to normal sera, K antigens were present in approximately normal amounts and L antigens in considerable excess. Dr. Morten Harboe and his associates confirmed these quantitative differences by immunoelectrophoresis using anti-(Fab')₂ antisera absorbed with type K and type L Bence Jones proteins to produce anti-type L and K specificities, respectively (methods similar to those described by Harboe, Deverill, and Godal, 1965). The precipitin arc in the IgG region produced by type L antisera was again heavy and showed localized deviation towards the antibody reservoir, whereas the relatively light arc produced by type K antisera had normal configuration, i.e. only type L antigens were detectable in the discretely migrating immunoglobulin fraction. The γ -globulins of the only sib, a healthy older brother, and of his parents had normal electrophoretic properties, and normal IgG levels were shown by immunological assays.

Genetic determinants (Moullec *et al.*, 1956).

Patient: —Gm a+, b+, c—, x—. Inv a—.

Both parents: —Gm a+, b+, c—, x+. Inv a—.

FIG. 5.—Electrophoresis of serum proteins, in each pair contrasting the patient's serum (below), containing a discretely migrating γ -globulin component, with pooled normal human sera (above). (a) Paper electrophoresis, patient aged 12 weeks; (b) starch gel (tris-borate buffer pH 8.6), post-mortem serum; (c) immunoelectrophoresis of post-mortem serum; antiserum with IgG specificity; IgG arc is distorted.

TABLE II
Immunoglobulins in Histologically-proven Thymic Aymphoplasia

Case Reference	Sex	Age at Death (mth.)	Immunoglobulins			Blood Lymphocytes Range/cu.mm.	Other Features	
			Age at Estimation (mth.)	IgG (mg./100 ml.)	IgA (mg./100 ml.)			
This report	M	5	5	1800 } (I)* 2400	180 (I)	2x (I) normal	790-6800	P†
Nezelof <i>et al.</i> (1964)	M	16	14	— (D)	— (N)	— (N)	0-840	C‡
Kadowaki <i>et al.</i> (1965)	M	16	12	314 (D)	142 (N)	169 (I)	3370-7030	
Fireman <i>et al.</i> (1966)	M	11	11	150 (D)	5 (D)	200 (I)	950-3800	
Fulginiti <i>et al.</i> (1966a) { Case 1	F	9	8	774 (N)	40 (N)	102 (N)	2500	P C
	F	16	16	902 (N)	46 (N)	123 (N)	304	
Schaller <i>et al.</i> (1966)	F	6½	4½ to 6	2500 (I)	390 (I)	13 (D)	900-6500	
Goldman <i>et al.</i> (1967)	M	29	21	363 (D)	450 (I)	145 (N)	256-6000	P C
Buckley <i>et al.</i> (1967)	M	9	9	18 (D)	24 (D)	71 (N)	268-2850	P
'Swiss-type' hypo-γ-globulinaemia ..				(D)	(D)	(D)		
Ataxia telangiectasia (most frequent pattern)				(N)	(D)	(N)		

* N, normal; D, decreased; I, increased (authors' interpretation).
† P, *Pneumocystis pneumonia*.
‡ C, Positive Coombs' test.

Antibodies. A myxovirus had been isolated from the patient's pharynx 8 weeks before death. No complement-fixing antibody to this virus was detected in the post-mortem serum. The blood groups of the patient and of the parents were all Group O D positive. No anti-A or anti-B isohaemagglutinins were detected in the patient's serum.

Discussion

The severe lymphoid depletion and dysplasia of epithelial elements in this infant's thymus are typical of the most frequently described congenital thymic abnormality, usually referred to as thymic aymphoplasia. Thymic aymphoplasia in early reports was associated with the severe impairment of cell-mediated and humoral immune reactions, short life-span, and lymphocytopenia of the 'Swiss-type' of hypo-γ-globulinaemia (Gitlin and Craig, 1963). However, our patient is at least the eighth now reported as having significant levels of one or more of the major serum immunoglobulin fractions IgG, IgM, or IgA, in the presence of histologically proven thymic aymphoplasia (Table II). Patients with the genetically distinct entity ataxia telangiectasia have been excluded from this list, as well as others with similar illnesses who have recovered or whose thymic deformities were less severe. The absolute levels of the immunoglobulins in these patients cannot be compared, because different methods were used for the quantitation, but on the basis of the authors' interpretation of these as normal, increased, or decreased, 7 patterns are apparent. All are different from that in our patient,

in whom all 3 components were increased, IgG in particular 4- to 5-fold over the mean level of normal infants of his age (Fulginiti *et al.*, 1966b; Stiehm and Fudenberg, 1966).
The more exceptional finding was that the greater part of his IgG had the electrophoretic properties of an M-type paraprotein. These proteins are rare in infancy, and it is of interest that an infant with paraproteinaemia, described by Stoop, Ballieux, and Weyers (1962), had severe lymphoid depletion in the thymus, spleen, and lymph nodes, and clinical features similar to the present patient. Stoop *et al.* could find only one previous description of an infant with paraproteinaemia. There have been few reports subsequently, and fewer where conformity with more recently defined M-type characteristics can be claimed from the demonstration of a great preponderance of one type of light polypeptide chain (Fahey and Solomon, 1963). The presence of large amounts of an M-type or 'monoclonal' protein in an adult would, in the first instance, require exclusion of myelomatosis or other malignancy. Myelomatosis does not appear to have been described in an infant, and, though plasma cells were abundant in our patient's tissues, they did not have neoplastic characteristics. On the other hand, children with thymic aymphoplasia are predisposed to lymphoid and lymphohistiocytic neoplasms (Peterson, Cooper, and Good, 1965; Goldman *et al.*, 1967), but the hyperplasia of reticular cells in our patient was clearly benign histologically and of a type also described frequently in thymic aymphoplasia.

Other changes in his lymphoid tissues, particularly depletion of lymphocytes and defective follicular development, were similar to those described in 'Swiss-type' hypo- γ -globulinaemia and, despite hyper- γ -globulinaemia, his clinical course was also in most respects typical of the 'Swiss-type' of immunological disorder (Rosen and Janeway, 1966). The presence of pneumocystis pneumonia is indicative of a severe immunological deficiency. Lymphopenia, though not now considered a consistent feature of the 'Swiss-type' disease, was present early in his illness. When the cases of thymic aymphoplasia in Table II are compared with the larger series reviewed by Haworth, Hoogstraten, and Taylor (1967), it is apparent that the presence or absence of immunoglobulins has had little effect on the course of their disease. The suggestion by Rosen and Janeway (1966) that all cases are manifestations of a single genetic entity affecting thymic development lacks confirmation. Sibs of 7 children with immunoglobulins listed in Table II had a history of a similar disease, but none were known to be hypo- γ -globulinaemic.

The failure of both endogenous and therapeutically administered immunoglobulins to modify the disease associated with thymic aymphoplasia could be due to dominance of associated defects in cellular immunity. Cell-mediated immune reactions were not investigated in our patient, but defects have been demonstrated in other cases with immunoglobulins (Schaller *et al.*, 1966; Buckley, Bradford, and Butcher, 1967). As an added factor, some of these cases with immunoglobulins appear to have a limited capacity for an antibody response. Our patient's serum did not contain antibodies to a recent virus infection. This might reflect the usual absence of demonstrable biological activity in M-type proteins, but even in the presence of adequate levels of electrophoretically normal IgG some children with thymic aymphoplasia have not developed antibodies against bacterial and viral antigens (Schaller *et al.*, 1966; Goldman *et al.*, 1967). Though these findings are consistent with the suggestion by Peterson *et al.* (1965) that normal development of the thymus is necessary for the recognition of antigenicity, the debilitated state of some patients may provide an alternative explanation. Furthermore, antibodies were demonstrated in the case reported by Nezelof *et al.* (1964).

Therefore, one possible explanation for immunoglobulin synthesis in some cases of thymic aymphoplasia and of the M-type proteinemia in our patient is an exposure to special antigenic stimuli not encountered by others. Both pneumocystis infection and auto-immune processes have to be con-

sidered in this role because each was present in several children listed in Table II. However, pneumocystis infection has been described in many persistently hypo- γ -globulinaemic cases; and the neonatal form of this infection, with an even more intense pulmonary plasmacytosis than that in our patient, occurs without an immunoglobulin response, or one limited to IgM (Ivdy *et al.*, 1967). Coombs positivity was demonstrated in 3 patients in Table II, including the only child with hyper- γ -globulinaemia comparable to that in our patient, and a similar association between auto-immunity and hyper- γ -globulinaemia has been described in the experimentally thymectomized animal (Sutherland *et al.*, 1965). Our patient, however, had no evidence of auto-immune disease.

Alternatively, previous authors have noted that the presence of immunoglobulins in some children with thymic defects is consistent with experimental evidence that the development of the immunoglobulin system is independent of the thymus (Di George *et al.*, 1967). Neonatal thymectomy in several species impairs cell-mediated immune reactions, whereas hypo- γ -globulinaemia has been produced only by ablation of other primary lymphoid organs (Peterson *et al.*, 1965; Miller, 1966). No comparable anatomical difference has been detected in cases of thymic aymphoplasia, which would correlate with their variable immunoglobulin synthesis.

As a further alternative, Kadowaki *et al.* (1965) have presented cytogenetic evidence to suggest that the immunoglobulins in their case of thymic aymphoplasia were the product of a graft of maternal immuno-competent cells. It was hoped that a similar origin of our patient's immunoglobulins would be excluded by the demonstration of paternal genetic determinants, but these investigations were frustrated by the parents having identical Gm and Inv types.

Precedents for the occurrence of M-type proteinemia in association with a congenital immunological deficiency state have been established in animals, in which the immunological defects were induced experimentally (Humphrey, Parrott, and East, 1964; Pierce, Chubb, and Long, 1966), and in man, following the grafting of lymphoid cells into an infant with 'Swiss-type' hypo- γ -globulinaemia (Harboe *et al.*, 1966). The explanation offered in each instance was that cloning of immunoglobulin-producing cell lines had limited subsequent synthesis to an abnormally homogeneous protein. The M-type proteinemia in our patient may have been the result of similar cloning occurring in the course of abnormal immunogenesis. A prerequisite for

such a theory is that individual immunoglobulin-producing cells are limited in their synthesis to a single type of light chain and single heavy chain, for which there is limited evidence in man (Bernier and Cebra, 1964).

Summary

Paradoxical hyper- γ -globulinaemia and tissue plasmacytosis were demonstrated in a 5-month-old male infant with thymic alymphoplasia. His death from *Pneumocystis carinii* pneumonia indicated an immunological deficiency state, while other features of his illness and the pathological findings in lymphoid tissues closely resembled those seen in the 'Swiss-type' of hypo- γ -globulinaemia. The serum immunoglobulin fractions IgG, IgA, and IgM were all increased, IgG 4- to 5-fold over the mean of normal infants in his age. The greater part of the IgG was electrophoretically homogeneous and was identified as a M-type or 'monoclonal' immunoglobulin with type L light chains. This rare occurrence of an M-type protein in an infant may have been the result of cloning of immunoglobulin-producing cells during the induction of his immunological deficiency state.

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