A Rare Case of Variable Immune Deficiency with Type II Dysgammaglobulinaemia, Light Chain Defect, Gut Associated IgA Deficiency and Progressive Neutropenia*

Kunal Saha, M.Sc., M.B.B.S., Ph.D.
Kamlesh Chopra, M.D.
Brig Rathindra Nath Dutta, M.B.

SUMMARY This report describes in detail an unusual variant of a common variable immunodeficiency disease in a seven-year-old boy. The unique features were progressive neutropenia due to defective myelopoiesis, serum IgG and IgA deficiencies, defective immunoglobulin light-chain synthesis, absence of secretory IgA and IgM gammopathy. He had been born healthy, but following a thermal injury at the age of 1½ years, he suffered recurrent attacks of sinopulmonary and urinary tract infections, enteritis due to enteropathogenic *E. coli, Giardia lamblia* and *E. histolytica,* developed pulmonary tuberculosis and died of deep mycotic infection of the oral cavity and obstruction of the bronchial tree. The cause of the defective myelopoiesis could not be determined, but it might have been due to prolonged sulphomamide therapy administered for controlling his persistent urinary tract infection due to paraphymosis.

ASIAN FACIFIC J ALLERG IMMUN 1985; 3:205-211.

Antibody-mediated (B-cell) immunity, cell-mediated (T-cell) immunity, phagocytic function and complement-mediated lysis are four major components of the immune system, which defend against bacterial, viral, fungal, protozoal and neoplastic agents. A deficiency in one or more of these systems may lead to local and systemic recurrent pyogenic or viral infections and growth failure.[1] Because of the extraordinary variability of immunological defects and dysfunctions, the majority of patients with immunodeficiency cannot yet be classified unequivocally and so they are grouped under the heading of variable immunodificiency.[2-5] In this communication we describe the case of a seven-year-old boy with progressive neutropenia due to maturation arrest at the myelocyte level, very low serum IgG and IgA levels, and the absence of secretory IgA. He had recurrent attacks of sinopulmonary and urinary tract infections, repeated enteritis due to enteropathogenic *E. Coli* infection and persistent intestinal infestations with *Giardia lamblia* and *E. histolytica.* He developed terminal IgM gammopathy and ultimately died of candidiasis of the oral cavity and bronchial tree. As far as we know, this is the first documented case of a rare variety of immune deficiency disease reported from the Indian subcontinent.[6-16]

CHRONOLOGICAL CASE HISTORY

The patient was born in 1975 by planned caesarean section. His parents had been married for 18 years. His birth weight was 6 lbs. The child had a normal development and weight gain. He had no adverse reaction following birth to vaccinations against smallpox, triple antigen and poliomyelitis; however, he had not been immunised against tuberculosis. He had paraphimosis since birth, which caused persistent urinary tract infections (UTI) from the age of six months. Trimethoprim – sulphamethoxazole was being administered for a long time to control his UTI. He had no other complaints except minor gastroenteritis at the time of teething and had an uncomplicated attack of measles at one year of age. When he was 1½ years old (1977), he suffered a

*From the Bacteriology Department, Govind Ballabh Pant Hospital, Paediatrics Department, Maulana Azad Medical College, and Armed Forces Transfusion Centre, Delhi Cantonment, Delhi, India.

thermal injury of his left hand. An indiginous ointment was applied to it, but the injury did not heal and became extensively infected. Thereafter, the patient developed a high fever and was treated with co-trimoxazole for 15 days along with the local application of framycetin. Since then he continued to have repeated attacks of diarrhoea, vomiting, tonsillitis, ear discharge, pneumonia and recurrent UTI. (This marked his *first crisis*) (Fig. 1). He developed dehydration due to the diarrhoea which was caused by enteropathogenic *E. Coli;* he was treated with gentamicin. In 1978, when the patient was 2½ years old, he was given a course of chloramphenicol to control his fever. Thereafter, he had epistaxis and lost weight. This was his *second crisis* (Fig. 1), which continued until 1980.

In 1979 he was hospitalised for high-grade fever (39.9°C), became unconscious, developed diarrhoea, vomiting, nasal bleeding, ear discharge; bronchopneumonia and UTI. He was treated with co-trimoxazole, erythromycin, penicillin and amoxycillin. A peripheral blood examination showed neutropenia. A bone marrow biopsy revealed the arrest of maturation of neutrophils at the myelocyte level (Fig. 2).

Since then the child continued to have repeated attacks of high fever, tonsillitis and cervical lymphadenopathy. In February 1980 leukaemia was wrongly diagnosed; he was given prednisolone and leukoran for two days only. He rapidly lost weight; developed diarrhoea and high fever, which subsided after the administration of cloxacillin and amoxycillin. An immunodeficiency disease was suspected. Serum immunoglobulin estimation showed IgG and IgA deficiency, but a normal IgM level (Fig. 1). Secretory IgA could not be detected in the saliva or stool. The patient was fed daily 20 ml of fresh human colostrum for five months. Injections of immunoglobulins (total 10 ml) were given over a period of six

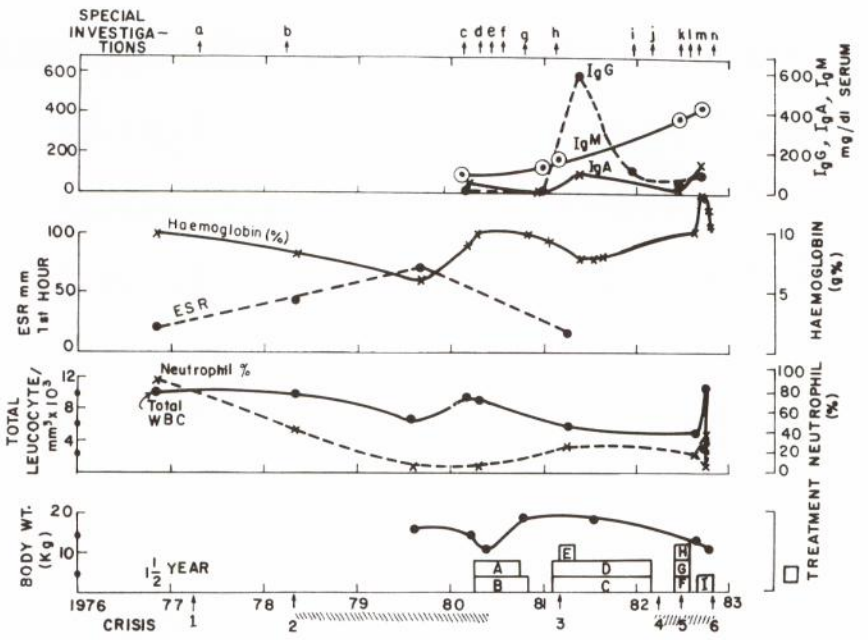

Fig. 1 Shows the clinical stages of illness. The haematological, immunological and other routine investigations as well as the treatment given to the patient are shown. Stool and urine tests among other routine investigations were performed for detecting bacteria and parasites etc. Body weights were recorded. Treatments given to the patient are shown chronologically (▭). The abcissa shows the period of illness and the number of crises (#). The hatched area (▨) shows periods of continuous illness.

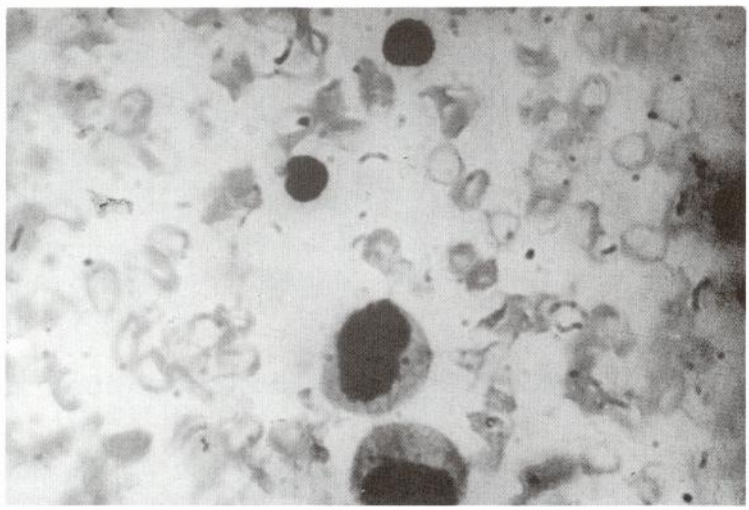

Fig. 2 The bone marrow (8 February 1980) was normocellular and normoblastic. The myeloid-to-erythroid cell ratio was 1.5:1. Reaction was normoblastic. There was an increase in the number of lymphocytes (33%). Myelopoiesis was arrested at the myelocyte stage, leading to neutropenia. The myelocytes were large and there were nuclear and cytoplasmic vacuolations. Megakaryocytes were adequate. Erythropoiesis was normal. No parasites were observed. The patient was given a corticosteroid stimulation test and peripheral blood examinations were performed every four hours, i.e. at 0, 4 and 8 and thereafter at 21 hours. At 0 hour the readings were: TLC 3,200/mm^3, DLC : P 2 L 78, M3, E4; at 4 hours; TLC 3100/mm^3, DLC: P 17, L 76, M3 E4; at 8 hours, TLC 3100/mm^3, DLC: p 16, L 81, M3, E nil; at 21 hours: TLC 5600/mm^3, DLC: P 11, L 83, M3 E 3.

months (Fig. 1). Thenceforth the patient showed an improvement in health and he gained weight. He remained well for 1½ months but had his *third crisis* in February 1981 (Fig. 1). He developed high grade fever, started bleeding nasally, became unconscious and developed pneumonia when he was rehospitalised (Fig. 3). He lost weight and was given gentamicin injections for 10 days but did not show any improvement. A tuberculin test was positive for the first time. Antituberculosis treatment (rifampicin and isonicotinic acid hydrazide) was started in February 1981 and was continued until May 1982 (Fig. 1). With this treatment the patient improved considerably, but still continued to have mild to moderate fever every other month, which was controlled by chemotherapy and antibiotics. During this period he was also given immunoglobulin injections (total 15 ml). The antitubercular treatment was discontinued in May 1982, when the patient had a *fourth crisis* (Fig. 1). He developed high-grade fever (39.9°C) and breathlessness, which were controlled by co-trimoxazole and salbutamol. In June 1982, the patient was taken to a sacred place and was given water to drink from a holy tank. Thereafter, he developed a violent *fifth crisis* (Fig. 1). He developed high-grade fever (41.2°C), tonsillitis, cervical lymphadenopathy, earache, swollen gums and oral thrush. His teeth decayed. His spleen became palpable. His condition deteriorated and he rapidly lost weight. A second bone marrow biopsy confirmed the earlier diagnosis of arrest of maturation of neutrophils at the myelocyte level (Fig. 2). However, the crisis was controlled by the intravenous injection of gentamicin and cloxacillin, the oral application of mycostatin, the injection of immunoglobulin (total 4 ml), the daily feeding, with fresh colostrum (20 ml), daily intravenous injection of vitamin B_{12} (1 mg) and oral folic acid therapy. He was discharged from the hospital, but within six days of discharge, he was rehospitalised with the *sixth and last crisis* (Fig. 1). He had high-grade fever (39.9°C), cervical lymphadenopathy, oral thrush (due to *Candida*) and gingivitis. Then he developed renal failure, Ludwig's angina, swelling of the face, neck and testes, and distention of the abdomen. The child was semicomatose and developed throat infection due to *E. Coli, Klebsiella* and *B. proteus.* Peripheral blood examination showed leucopenia and neutropenia. Myelocytes appeared in the peripheral blood. A radiograph of his chest showed atelectasis of the right lower lobe. The liver was palpable 3 cm below the costal margin. The patient developed terminal jaundice and died.

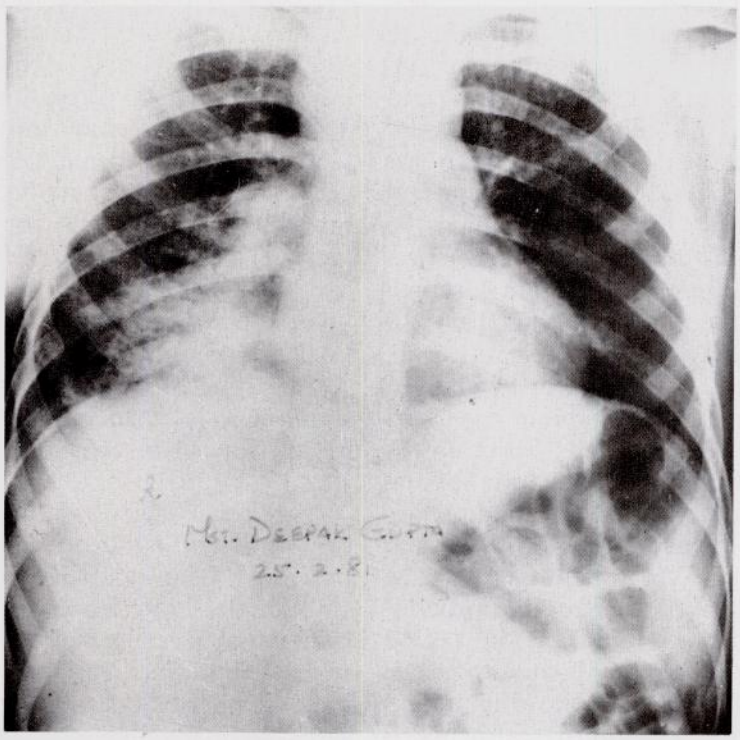

Fig. 3 Chest radiograph (February 1981) shows evidence of pneumonia.

FAMILY HISTORY

The father and sister of the patient were healthy, but his mother had bronchial asthma since she was 20 years of age. Her asthma had been controlled by bronchodilator drugs, prednisolone and aminophylline (theophylline ethylene diamine). The patient's maternal grandmother and maternal great-grand mother had also bronchial asthma. One of the patient's maternal aunts died of pneumonia at the age of 1½ years; she had had recurrent attacks of pneumonia and growth failure. One maternal uncle of the patient died at the age of two years due to a brain tumour. The serum immunoglobulin and complement levels as well as the T- and B-cell counts of the patient's father, mother and sister were all within normal limits. There was no history of consanguineous marriage.

Special investigations and immunological tests and management (Fig. 1):

The chronological investigations performed and the treatments administered are shown in Figure 1. The child had his first crisis in 1977 and a subsequent episode in 1978. During the time between the crises, the patient was chronically ill (shown by the shaded area in the abcissa of the accompanying graph).

The ensuing attacks were more frequent and the child began to lose weight progressively. His total leukocyte count gradually decreased from 1977 onward; the haemoglobulin level was moderately low. Both of these parameters showed some increase between the second and third episodes. Interestingly there was a parallel increase in body weight, a rise in the percentage of neutrophils, a concomitant fall in the erythrocyte sedimentation rate, and an increase in the haemoglobin level.

The child had not been given BCG vaccination during infancy and, until 1980, he was tuberculin-unresponsive. However, in 1981, he showed positivity to a tuberculin test and had consolidation in his lung, which was suggestive of tuberculosis. He was dinitro-chlorobenzene (DNCB)-responsive. The terminal rise of the leukocyte count and haemoglobin level were due to fresh blood and buffy coat transfusions (treatment I).

After feeding of colostrum (20 ml daily) (treatment A) and subsequent intramuscular injections of immunoglobulin (25 mg/kg/week) (treatment B), the child gained weight (20 kg); he became active and had regular bowel movements (Fig. 1). His condition stabilised following the antituberculosis treatment (treatment C) and immunoglobulin injections (treatment D). Repeated stool examinations from 1977 to 1981 (special investigations a, b, c, d, f and g, Fig. 1) showed persistent enteropathogenic *E. Coli* (untypable) infection, *E. histolytica* (vegetative form) and *Giardia lamblia* (cyst) infestations, as well as the presence of red blood cells (RBCs) and pus cells. The intestinal infections were resistant to all conventional antibiotic and antiparasitic treatments. However, they could be eradicated with prolonged metronidazole therapy (treatment E) along with colostrum feeding (treatments A and G). It is noteworthy to mention here that secretory IgA could not be detected in his saliva and stool (special investigation d, Fig. 1). Since birth, the child had paraphymosis and had been suffering from persistent UTI from 1977 until the time of his death. His urine showed albumin, pus cells, RBCs, granular casts, *E. Coli* and *B. proteus* (special investigations a, f, i and j, Fig. 1). In the end, he developed renal and hepatic failure, infection of the mastoid bone due to *Pseudomonas, E. Coli* and *Streptococcus,* fungal granuloma of the hard palate leading to palate perforation and terminal candidiasis of the bronchial tree resulting in bronchial obstruction. Antifungal drugs such as mycostatin and nazarol (50 mg) orally were given daily (treatment H, Fig. 1). Although the child had been suffering from repeated and persistent infections of the respiratory, gastrointestinal and urinary tracts since 1977, his immune deficiency state was diagnosed for the first time in 1980, when his serum IgA and IgG levels were found to be very low (both less than 8 mg/dl) (special investigation Number c, Fig. 1). However, at that time he had an adequate serum IgM level (134 mg/dl) (special investigation c, Fig. 1). The serum levels of IgG and IgA increased after the injections of immunoglobulin (treatments B, D and F) (Fig. 1), but those rises were not sustained. Curiously there was a progressive rise in the serum IgM level, which was 400 mg/dl at the time of his death (special investigation k, Fig. 1). The slight terminal rise in the serum IgG (100 mg/dl) and IgA (95 mg/dl) levels was probably due to the transfusions of fresh blood (three units), plasma (one unit), buffy coat (three units), the intramuscular injection of immunoglobulin and the administration of gentamicin, cloxacillin and ampicillin (treatment I). The percentage of neutrophils progressively decreased during the period from 1977 to 1980, but the level increased a little following immunoglobulin therapy (treatments B and D). His neutropenia did not respond to vitamin B-12 injection and oral folic acid therapy (treatment H). His blood B-cell percentage (tested in 1981) was adequate (23%), but his T-cell percentage was low (23%) and the null cell percentage was 54 per cent. A tuberculin test was negative in 1980 (special investigation d, Fig. 1), but later it became positive (special investigation f, Fig. 1). A chest radiograph showed right lung consolidation, but his sputum did not show the presence of acid-fast bacilli.

The patient had a light chain-defect. The K (kappa) chain was not detected in his serum and the λ (lambda) chain level was low (special investigation e, Fig. 1). His natural antibody levels (A.S.O. titre and blood group iso-agglutinins) were within normal limits (special investigation b, Fig. 1). He showed immune Schick test and high titre (1:8,192) antibody against *E. histolytica* (special investigation e, Fig. 1). The low serum C3 (20 mg/dl) and C4 (8 mg/dl) levels in 1980-1981 (special investigation e, Fig. 1) and high circulatory immune complex at the terminal stage (0.09 mg/dl) (special investigation k, Fig. 1) could have been due to complement activation by various infectious agents and circulatory immune complex formation. The appearance of serum antinuclear factor during 1980 and 1982 (special investigations e and k, Fig. 1) might have been due to the impairment of suppressor T-cell function and the dysfunction of the thymic micro-environment leading to the loss of immune homeostasis.[17,18] At the time of death, the patient's serum C3 level increased to 112 mg/dl (special investigation k, Fig. 1).

Two bone marrow biopsies, one performed in 1980 and the other in 1982, showed adequate erythropoiesis, lymphopoiesis, thrombopoiesis, but defective myelopoiesis (Fig. 2). Peripheral blood pictures seen on several occasions were parallel to that of the bone marrow histology and showed

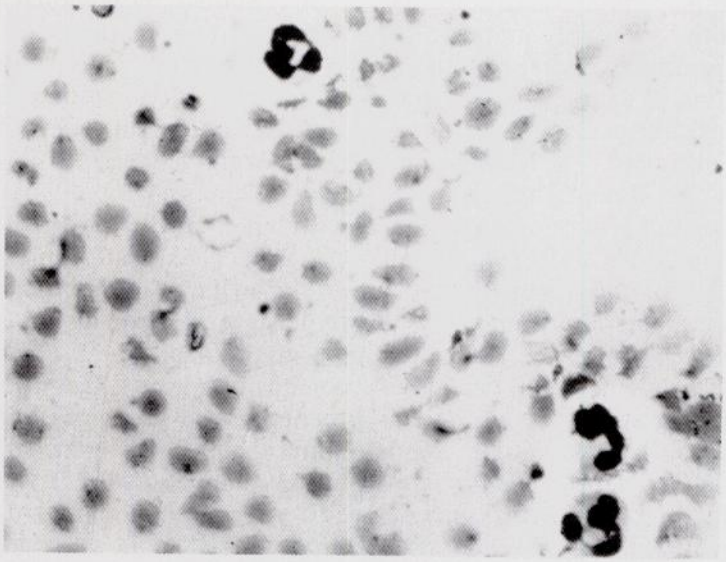

Fig. 4 A peripheral blood smear during terminal illness shows juvenile and hypersegmented neutrophils, suggestive of vitamin B_{12} deficiency.

normocytic and mild hypochromic RBCs. The patient never became severely anaemic; his platelets were always adequate, but his neutrophil counts were very low and there was compensatory lymphocytosis (special investigation c, Fig. 1). A corticosteroid stimulation test confirmed the existence of defective myelopoiesis (Fig. 2). Terminally, his RBCs showed mild to moderate microcytosis and hypochromia; polymorphonuclear leukocytes showed hypersegmentation which was suggestive of vitamin B-12 deficiency (Fig. 4); platelets were adequate and 2% myelocytes were seen in peripheral blood. Jaundice developed at the time of death. Serum bilirubin was 7.6 mg/dl; SGOT and SGPT were 150 and 280 units respectively. Australia antigen was not found. Coombs test was negative. Renal failure started and the blood urea level increased from 65 mg/dl to 130 mg/dl. Serum creatinine was 2 mg/dl; serum electrocytes were Na 140 mMol/1; K3 mMol/1. Terminal fever was in the range of 39°C to 37°C.

DISCUSSION

Neutropenia with hypoglobulinaemia in infants and children has been reported. About 50 per cent of those young patients have had familial and sex-linked recessive transmission; the same syndrome may occur in both sexes, but with no evidence of genetic transmission. In these patients, there is an unusual history of frequent bacterial infection and death occurring during the first few years of life. The spleen may be slightly enlarged. Neutropenia is moderate to severe and may be associated with compensatory monocytosis in some patients. Usually there is an increase in the number of neutrophils in response to infection. There is an abundance of early myeloid forms in bone marrow. The serum IgG and IgA levels are low, but that of IgM is high. Neutropenia may disappear after administering an injection of immunoglobulin, which suggests the possibility of a plasma factor deficiency being responsible for neutropenia. Leukocytotoxic factors, such as leukocyte autoantibody, will accelerate the removal of granulocytes from the blood and eventually produce bone marrow exhaustion.[19] Most cases of agammaglobulinaemia with immunoglobulin-bearing B-lymphocytes have a similar history of recurrent infections beginning several years after birth.[20]

The clinical features of our patient were somewhat similar to those described by the above authors. The patient was born healthy and had a normal development until he reached the age of 1½ years. Thereafter, he began suffering from recurrent infections. His family history was unremarkable for immunodeficiency and auto-immune disease. However, there was a history of infant death, malignancy and atopic diseases in the family.

A history of smallpox vaccination during infancy without any adverse reaction as well as an uncomplicated attack of measles at the age of one year suggested that the patient had intact thymic functions and could mount cell-mediated immunity at that time. This observation gets further support from the fact that he responded to DNCB at the beginning of his treatment and showed tuberculin conversion in 1981. Thereafter, his T-cell count decreased considerably; he developed pulmonary tuberculosis which responded to antituberculosis treatment. During his terminal illness in 1982, when he was DNCB-unresponsive, he succumbed to an overwhelming deep mycotic infection of the oral cavity and bronchial tree. Thus, at the onset of illness in 1977, our patient might have had a functioning cellular immune system, but thereafter, because of progressive neutropenia, he developed recurrent attacks of severe, uncommon, suppurative, sinopulmonary and urinary tract infections due to pathogenic as well as opportunistic micro-organisms. As a result of the repeated infections, his cellular immunity was exhausted, leading to terminal deep mycosis and death.

Geha *et al*[21] reported 19 cases of common variable agammaglobulinaemia, 15 of which had either normal or increased B-cell counts. The percentage (23%) of B cells in our patient was within normal limits. Thus the low level of IgG

and IgA, and the normal level of IgM in the serum of our patient might have been due to the inhibition of B-cell differentiation[22] (M-G- A switch hypothesis) because of the presence of suppressor T cells. Waldman *et al*[23] demonstrated T-suppressor cells in five out of eight cases of common variable hypogammaglobulinaemia. We, however, had not studied T-cell subsets in our patient.

Besides the remarkable dysgammaglobulinaemia that this patient had had, another spectacular finding was progressive leukopenia and neutropenia. This might have resulted in decreased phagocytosis and the killing of bacteria,[24] leading to the persistent, usually suppurative infections of the respiratory and urinary tracts. This probably exhausted the patient's T-cell immunity, leading to terminal deep mycotic infection.

We do not know the exact cause of this neutropenia. The child had paraphimosis since birth. He had repeated urinary tract infections and was given co-trimoxazole and chloramphenicol repatedly for a very long time. We believe that the persistently defective myelopoiesis in our patient might have been iatrogenic and the profoundly low serum IgG and IgA levels might have been congenital. There are reports that certain drugs, notably phenytoin sodium and penicillamine, can induce selective IgA deficiency.[20]

During his early life, the child was probably protected by the umbrella of maternal IgG that he had inherited transplacentally. When he was 1½ years old, he suffered a burn injury on one of his limbs and it became badly infected. The healing of the injury was delayed probably owing to the absence of his own IgG. Although he had an adequate serum IgM level, it was mostly intravascular. Thereafter he had six moderate to severe crises due to sinopulmonary infections.

Because of the lack of information on definite patterns and causes, we have classified the immune deficiency state of our patient within a variable immune deficiency group, which presumably includes many syndromes. Included in this group are patients previously classified as having congenital, non-x-linked, hypogammaglobulinaemia, primary dysgammaglobulinaemia (of both childhood and adult life) and acquired primary hypogammaglobulinaemia. But the striking disorders associated with the dysgammaglobulinaemia in our patient were defective myelopoiesis and the absence of gut-associated IgA deficiency. As far as we know, the three aforementioned deficiencies found in our patient have been documented for the first time.

The presence of serum antinuclear factor, abnormal immunoglobulin concentrations with IgM (K) proteinaemia, a history of recurrent infections, growth failure and the death of his aunt during infancy as well as a history of malignancy in his uncle suggested a hereditary influence.[20] However, it was not possible to make detailed studied of gene defects of the Gm and InV markers in the immunoglobulin synthesis in the family members.

Hobbs has described eight types of dysgammaglobulinaemia. According to his description, the dysgammaglobulinaemia in our patient was the rarest form: Type II.[25] The absence of a K-chain in our patient is interesting. In normal individuals, the K/ λ ratio of serum immunoglobulins has been reported to show an almost constant value, which differs among races. A disproportionate K/λ ratio and even the absence of a K-chain have been reported to occur in various forms of primary immunodeficiency diseases with diarrhoea and recurrent respiratory infections.[26] On this basis, a light chain-deficiency is viewed as a variant of common variable hypogammaglobulinaemia.[27]

Childhood M-proteinaemia has been associated mostly with immunodeficiencies. Terminally, our patient had developed IgM (k) M-protein. Similar monoclonal gammopathy had been described earlier in Wiskott-Aldrich syndrome, severe combined immunodeficiency and Nezalof syndrome.[26] Our patient would appear to fit the pattern of immunoglobulin deficiency, with an increased level of IgM in the WHO classification.[28] Goldstein *et al*[29] have described acquired hyper-IgM syndrome with necrotising granuloma, which could be reconstituted by gammaglobulin therapy without complication. The immunoglobulin abnormalities recognised in our patient were of an extreme variety, similar to a disproportionate K/λ ratio, imbalance of the immunoglobulin classes and an absence of gut-associated IgA. In our patient, the temporary improvelopment in neutropenia following the injection of immunoglobulin (Fig. 1), was described earlier.[19] However, the exact mechanism of improvement is not known.

Our patient had recurrent, crippling sinopulmonary and gut infections and had no detectable secretory IgA. As no means exist for providing secretory IgA antibody to his mucous membranes, we decided to administer fresh colostrum, the freeding of which showed some benefit (Fig. 1). Colostrum and breast milk appeared to provide important immune defenses for the IgA-deprived gastrointestinal tract of the child.[30]

ACKNOWLEDGEMENTS

The authors are thankful to Dr. S.K. Sood, Professor of Pathology, University College of Medical Sciences, Delhi and Dr. S.K. Jain, Lecturer of Pathology, Maulana Azad Medical College, Delhi, for their expert opinion concerning the haematological aspects of the study. They are indebted to Colonel K.N.P. Sinha, Senior Advisor and Clinical Immunologist, Army Hospital, Delhi Cantonment 110010, for performing some of the immunological investigations.

Thanks are also due to Dr. M.D.

Cooper and Dr. R.K. Chandra of the U.S.A., who had examined the patient during his visit to Delhi in 1982 at which time they gave us valuable suggestions about the management of their case.

REFERENCES

1. Ammann AJ, Fuddenberg HH. Immunodeficiency diseases. In: Fudenberg HH, Stites DP, Caldwell JL, Wells JV. eds, Basic and clinical immunology. Maruzen: Lange Medical Publication Asia Edition, 1980: 409.
2. World Health Organization. Memoranda. Primary immunodeficiency. Bull Wld Hlth Org 1971; 45:125-42.
3. World Health Organization Scienctific Group. Immunodeficiency. Wld Hlth Org Tech Rep 1978; Entire issue.
4. Stiehm ER, Fulginiti VA. (eds.) Immunologic disorders in infants and children. Philadelphia: WB Saunders 1980: Entire issue.
5. Ammann AJ, Fudenberg HH. Evaluation of infants and children with recurrent infection. Curr Probl Pediatr 1975; 5:Entire issue.
6. Mehta BD, Patel JC, Stor SD, *et al.* Hypogammaglobulinaemia; A report of 2 cases. Ind J Med Sci 1970; 24:809.
7. Chandra RK. Transient hypogammaglobulinemia in a child. Ind J Pediatr 1970; 37:418-21.
8. Mehta BC, Athawale VB, Baxi AJ. Hypogammaglobulinemia in a child. Ind J Pediatr 1970; 37:332-6.
9. Indamdar S, Trivedi SK, Dabke AT. Congenital hypogammglobulinaemia. Pediatr Clin Ind 1973; 8:96.
10. Datta BN. A case of vaccinia gangrenosa: Weekly Staff Clinicopathological Conference. Bull Postgrad Inst Med Sci Chandigarh 1975; 9:161.
11. Chandra RK, Ghai OP. Primary immunodeficiency states in Indian children. Indian J Med Res 1976; 64:68-75.
12. Malaviya AN, Rajagopalan P, Taneja RL. Pattern of primary immunodeficiency seen in India. J Assoc Phys India 1977; 25: 465.
13. Rajarajeshwari G, Vishwanath J. Bruton's disease. A case report with unusual findings. Indian Pediatr 1978; 15:67.
14. Seth V, Malaviya AN, Rajagopalan P, Ghai OP. Progressive vaccinia successfully treated with vaccinia immunoglobulins. Indian Pediatr 1978; 15:67-70.
15. Mehta BG, Agarwal MB, Sanzgiri PS. A patient of selective IgG deficiency. J Assoc Phys India 1981; 29:159-63.
16. Saha K, Chopra K. Primary immune disorder in children and their diagnosis. J Commow Dis 1984; 16:11-7.
17. Waldmann TA, Strober W, Blease RN. T and B cell immunodificiency diseases. In: Parker WC, ed, Clinical immunology. Philadelphia: WB Saunders, 1980:314.
18. Chudwin DS, Cowan MJ, Wara DW, Ammann AJ. Patients with abnormal proportions of T lymphocyte subsets have reduced *in vitro* cellular immunity. Clin Immunol Immunopath 1983; 26:126-36.
19. Huston DP, Smathers PA, Reeves JP, Steinberg AD. Effects of the thymic microenvironment on autoantibody production in (NZB X NZW) F_1 mice. Clin Immunol Immunopath 1983; 26:91.
20. Cooper MD, Bucklay RH. Developmental immunology and the immune deficiency diseases. JAMA 1982; 248:2658-69.
21. Geha RS, Schneeberger E, Merler E, Rosen FS. Heterogeneity of "acquired" or common variable agammaglobulienia. N Engl J Med 1974; 291:1-10.
22. Reinherz EL, Schlossman SF. Regulation of the immune response inducer and suppressor T-lymphocyte subset in human beings. N Engl J Med 1980; 303:370-3.
23. Waldman TA, Durm M, Broder S, Blackman M, Blaese RM, Strober W. Role of Ts cells in pathogenesis of common variable hypogammaglobulinaemia. Lancet 1974; 2:609-13.
24. Dossett JH. Microbial defenses of the child and man. Pediatr Clin North Am 1972; 19:355-72.
25. Hobbs JR. Immune imbalance in dysgammaglobulinaemia type IV. Lancet 1968; 1: 110-4.
26. Kawai T. Immunoglobulin abnormalities in primary immunodeficiency. Aust Famil Physician 1978; 8(Special issue):42-9.
27. Cruz, JR, Carlsson B, Garcia B, *et al.* Studies on Human milk (I). Secretory IgA quantity and antibody levels against *Escherichia coli* in colostrum and milk from under priviledged and privileged mothers. Pediatr Res 1982 16:272-6.
28. Rosen FS, Wedgwood RS, Aiuti F, *et al.* Primary immuno deficiency diseases. Report prepared for the WHO by a Scientific Group on Immunodeficiency. J Clin Immunol Immunopath 1983; 28:450.
29. Goldstein MF, Kornstein MJ, Talbot S, Levinson AI. Acquired hyper-IgM syndrome with necrotising granuloma. J Allergy Clin Immunol 1985; 75:472-8.
30. Fulginiti VA. Immunoglobulin. In: Fulginiti VA, ed, Immunization in clinical practice. Philadelphia: Lippincott Co, 1982: 221-36.