The Seoul Journal of Medicine
Vol. 28, No. 3:281-286, September 1987

Immunodeficiency with Hyper-IgM (Dysgammaglobulinemia Type I) Accompanied by Aortic Calcification

Dong Kyu Jin, Hoan Jong Lee, Hyo Seop Ahn, Yong Choi, Hyung Ro Moon, Chul Woo Kim*, Je G. Chi*, Myoung Hee Park** and Eung Soo Whang***

Departments of Pediatrics, Pathology, Clinical Pathology**, Microbiology***, College of Medicine, Seoul National University, Seoul National University Children's Hospital, Seoul 110, Korea*

=Abstract=Immunodeficiency with hyper Ig-M (dysgammaglobulinemia type 1) is characterized immunologically by decreased or absent serum levels of IgG, IgA, but elevated or normal IgM. First described by Rosen *et al.* in 1961, the syndrome is usually seen in young boys with recurrent bacterial infection, and autoimmune diseases are the frequent manifestation.

We present a 4 9/12 year old boy who showed imnunologic findings compatible with immunodeficiency with hyper-IgM and associated with huge dilatation and calcification of the aorta. We studied the B and T cell function in vitro which suggested the excessive suppressor function of the patient's T lymphocytes, although special staining of the lymph node did not show predominant suppressor population.

Key words: ***Immunodeficiency, Dysgammaglobulinemia, Aortic calcification***

INTRODUCTION

This rare disease in young boys is characterized by immunoglobulin profile of decreased or absent serum levels of IgG and IgA but elevated or normal IgM. Recurrent bacterial infections including otitis media, pneumonia, tonsillitis characterize the disease. In addition to unusual susceptibility to infection, some of these patients may present with thrombocytopenia, hemolytic anemia, nephritis and arthritis, possibly representing manifestations of autoimmune process(Goldman *et al.* 1976).

We present a Korean boy who showed immunoglobulin abnormalities compatible with dysgammaglobulinemia type I, associated with hypertension and aortic clacification.

CASE REPORT

A 4 9/12 year old boy was admitted to pediatric ward, Seoul National University Children's Hospital for evaluation of enlarged neck mass. At 7 months of age intermittent yellowish ear discharge developed with posterior cervical lymph node swelling. Then he suffered from frequent bouts of pneumonia which was relieved by antibiotics and was frequently complicated by intermittent ear discharge. Six months prior to admission his mother found a large neck mass. He was admitted for evaluation of the mass on November 6, 1982.

He had two healthy sisters, 7 and 10 years old. Physical examination showed a stout boy. The blood pressure was 100/70 mmHg, the heart rate 100/min, and the respiratory rate 24/min. Body weight and height were 13.8Kg and 94cm respectively which related to 10-25 percentiles. His forehead protruded and nasal bridge was flat. Tonsils were moderately enlarged and nodular. Both ear drums were perforated. There was a 6×4 cm movable slightly tender mass located in the right submandibular area and a 3×2 cm mass in the left infraauricular area. There were also a few lymph nodes in the inguinal and axillary area. The chest and the abdomen findings were unremarkable. The laboratory findings included the hemoglobin 12.2 gm%, the white cell count 16,600/mm^3 and the platelet 146,000/mm^3. The urine analysis and the blood chemistry were unremarkable. The heterophil antibody was negative. The bone marrow aspiration showed hypercellular marrow with granulocytic hyperplasia. Biopsy of the cervical lymph node re-

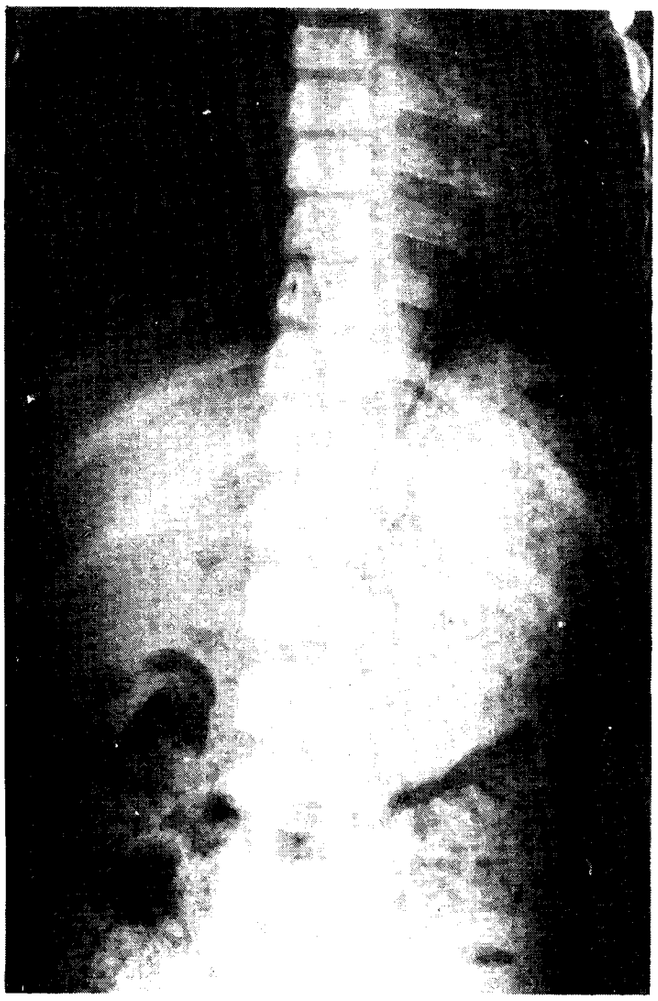

Fig. 1. X-ray finding of simple abdomen revealed linear calcification along the aortic border.

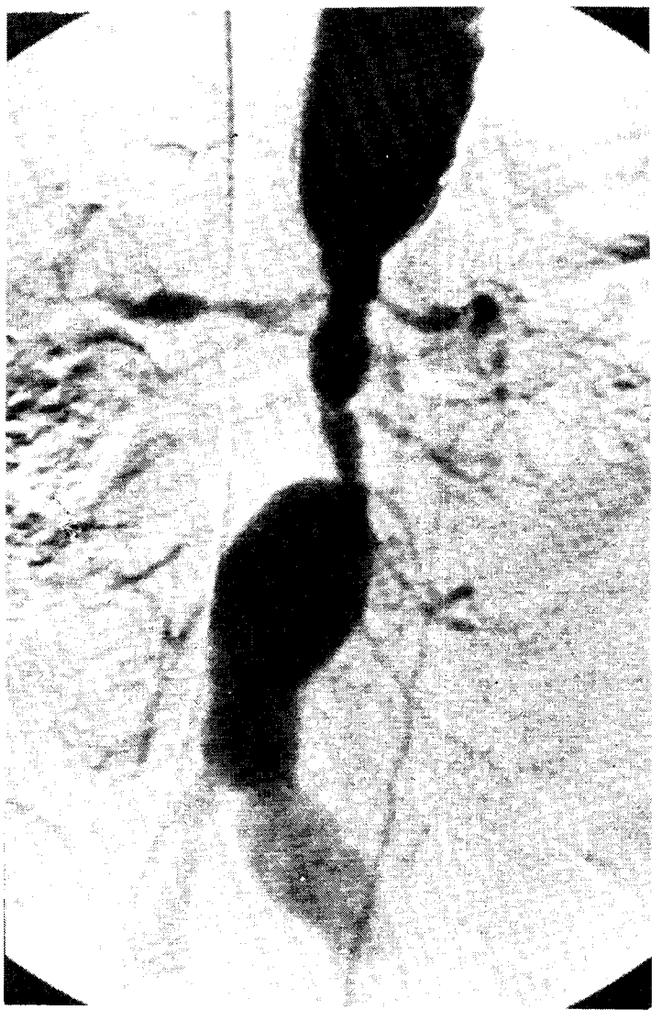

Fig. 2. Digital subtraction angiography showed normal upper and middle thoracic aorta, but fusiform dilatation of lower thoracic and upper abdominal aorta.

vealed follicular hyperplasia. P.N.S. view showed haziness in maxillary and ethmoid sinuses. Four years later he was readmitted to this hospital because of dyspnea and headache for 1 month. The physical examination showed chronically ill looking boy, the blood pressure was 200/160 mmHg, the heart rate 104/min, the respiratory rate 30/min, the body temperature 37°C. The lymph node of the neck was thumb tip sized. The liver was 2 1/2 finger breadth palpable below the costal margin. The spleen was not palpable. The laboratory finding included hemoglobin 10.1gm%, the white blood cell count 13,300/mm^3, the platelet count 386,000/mm^3. The WBC differential count was; segmented neutrophil 54%, lymphocyte 35%, monocyte 5%, eosinophil 6%. Total eosinophil count was 1452/mm^3. Urine analysis was normal. BUN was 7mg%, creatinine 0.4mg%. plain X-ray of the abdomen showed remarkable finding(Fig. 1) of linear calcification along the aortic border. Digital subtraction angiography revealed normal upper and middle thoracic aorta, but narrowing and fusiform dilatation of lower thoracic and upper abdominal aorta (Fig. 2).

His immunoglobulin status is summarized in Table 1. Peripheral small lymphocyte number was adequate, and eosinophilia was noted. DNCB skin stimulation test showed sensitization after 2 days. But Mantoux test was negative despite of previous B.C.G. vaccination. Sheep RBC T-rosette was 69%. Helper and suppressor T cell ratio was reversed, and repeated test showed similar result.

Lymphocyte culture studies showed increased spontaneous blastogenesis and phytohemagglutinin stimulated blastogenesis was slightly imparied (Table 1). Serum immunoelectrophoresis showed single arc of IgM in the trivalent antiserum. There

Table 1. Immunologic status of the patient

T cell	
1. peripheral blood lymphocyte number	5,300/mm^3
2. Mantoux test	negative
3. DNCB skin test	sensitized
4. sheep RBC rosette formation	69%
5. PHA stimulation test	slightly decreased(Table 2)
6. T3/T4/T8	83/ 9/56(%)
	77/22/53(%)
B cell	
1. IgG/IgA/IgM/IgD/IgE	1.0 /1.0 /392/5.8(mg/dl)/18(IU/ml)
2. isohemmaglutinin (anti-B)	1:1
3. immunoelectrophoresis	no IgG and IgA fraction, IgM single arc
4. pokeweed mitogen stimulation	no IgG and IgA production
	normal IgM production

Table 2. Mitogen stimulated lymphocyte culture (H3-thymidine uptake 72 hours culture)*

cpm(stimulation index)

	Patient	Control 1	Control 2	Control 3
unstimulated	5,528	1,270	1,685	1,017
PHA-M 5 μg/ml	6,377(1.1)	4,813(3.7)	25,328(15.0)	3,055(3.0)
PHA-M 20 μg/ml	26,279(4.7)	40,379(31.7)	71,445(42.4)	24,605(24.1)
PHA-M 100 μg/ml	71,437(12.9)	34,481(27.1)	69,899(41.4)	90,552(89.0)

* Patient's spontaneous(unstimulated) blastogenesis is unusually high. PHA stimulated blastogenesis is slightly impared, more evident in low and medium doses of PHA.

were no precipitin arcs in the monovalent antisera of IgG and IgA. Immunogobulin quantitation by radial immunodiffusion showed elevated IgM (392 mg/dl). Anti-B isohemmaglutinin titer was 1:1. IgM antibody against rubella was positive at 1:44. Complement profile was normal(C3/C4/CH50=57.9mg/dl/53.7mg/dl/16.3 U/ml) and NBT score was 12%.

Lymph node biopsy showed widening of paracortical area with aggregates of moderate to large sized lymphocytes and focal small areas of necrosis. Scattered small secondary lymphoid follicles in which active phagocytic activity was noted(Fig. 3). In marker study, a few B-cell aggregates were observed in peripheral location(Fig. 4). Pan T-lymphocyte(Dako, T-1) were diffusely distributed in the widened paracortical areas(Fig. 5). T8 lymphocytes were also scattered in the paracortical areas, but far less in numbers than T1 positive cells(Fig. 6).

We also studied the B and T cell function in vitro. Peripheral mononuclear cells were separated using centrifugation on Ficoll-Hypaque gradients. T cells were separated from non-rossette forming cells. Patient and control T cells and B cells were separated, and cultured in various combinations. Immunoglobulin production, which require cooperation between T and B cells, was assessed by culturing cells for 5 days with pokeweed mitogen and then determined the secreted immunoglobulin by ELISA method. Patient B cell secreted negligible amount of IgG and IgA at any combination with his T cell concentration, but IgM secretion was normal, and when patient T cells were added to the control B cells instead of control T cells, slight decrease in IgG production was noted(Fig. 7).

The control of blood pressure was started with captopril 25mg t.i.d, Inderal 10mg q.i.d, and Esidrex 25mg t.i.d. But BUN and creatinine became elevated, and Minipress was substituted for captopril. The blood pressure then stabilized around 140/95. We also started monthly immunoglobulin replacement as is given in agammaglobulinemia.

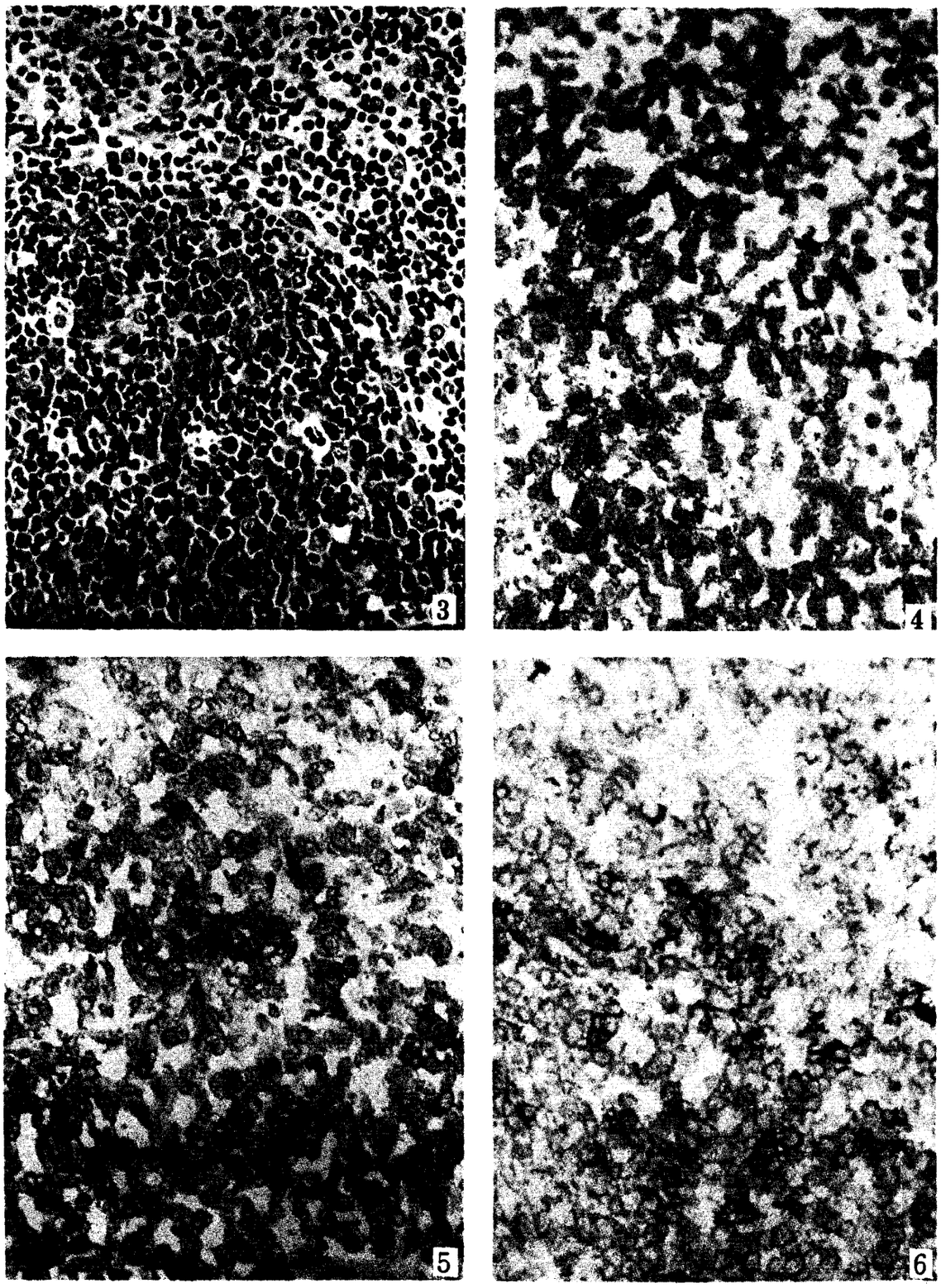

Fig. 3. Lymph node section showed reactive formation of germinal center and widening of parafollicular area (Hematoxylin and eosin staining, x200).

Fig. 4. Pan B lymphocytes (B) were localized in the area, which is suggestive of germinal center in Fig. 3 (Pan B, immunoperoxidase, x200).

Fig. 5. Pan T lymphocytes(T1) were diffusely distributed in the widened paracortical areas (T1, immunoperoxidase, x200).

Fig. 6. Suppressor lymphocytes(T8) were also scattered in the paracortical area, but far less in numbers than the T1 positive cells (T8, immunoperoxidase, x200).

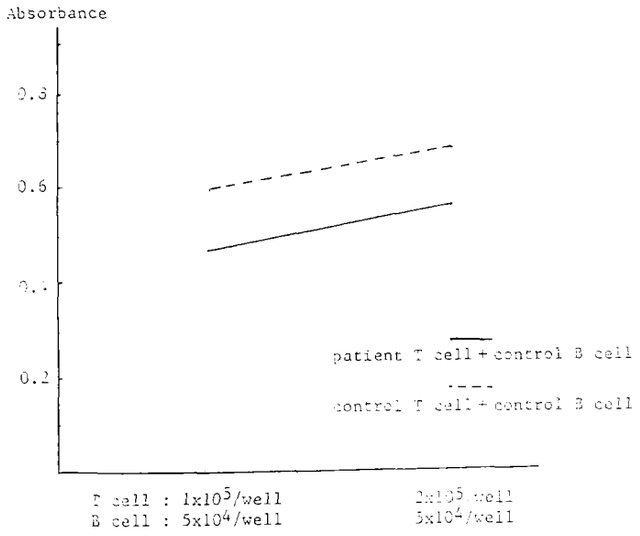

Fig. 7. When patient T cells were added to the control B cells instead of control T cells, decrease in IgG absorbance was noted.

DISCUSSION

First described by Rosen *et al.* in 1961, immunodeficiency with hyper-IgM is usually seen in young boys, and an X-linked mode of inheritance has been established in several families. It is characterized immunologically by decreased or absent serum levels of IgG, IgA, but elevated or normal IgM. In this patient, it is not certain whether he had immunologic dysfunction prenatally or postnatally and we could not find the genetic predisposition. But nearly absent serum level of IgG, IgA and elevated IgM rule out the possibility of common variable immunodeficiency and agammaglobulinemia. So we categorized him into immunodeficiency with hyper-IgM which was previously known as dysgammaglobulinemia type 1.

Phylogenetically IgM is the first surface immunoglobulin synthesized by B lymphocytes. Each B lymphocyte begins by synthesizing IgM class immunoglobulin, and, after a number of cell divisions some progeny of that clone may undergo a switch from IgM to IgG, and it may be this point which disturb the immunologic status of this syndrome.

Krantman *et al.* (1978) reported T and B cell function abnormalities in 3 boys with immunodeficiency with hyper-IgM. According to this report, addition of T cells from 2 patients to normal B cell supressed immunoglobulin synthesis, but 1 patient had normal T and B cell activity. So they concluded that defective differentiation of B cells into immunoglobulin producing cells was a constant feature and excessive T supressor activity was a variable accompanying abnormality.

We also cultured the B lymphocyte in this patient. Only IgM but no IgG or IgA was detected in the culture medium, which was a compatible finding with the experiment of Krantman. Reversed T4/T8 ratio in this patient suggested the increased suppressor function or decreased helper function. Although we failed to quantitate, the IgG absorbance showed the difference between patient and control, which was suggestive of excessive suppressor activity (or decreased helper activity) of T lymphocytes. But we couldn't find the dominant suppressor population in the special staining of the lymph node.

Recent observations have indicated that disorders of the immune system must be added to the spectrum of congenital anomalies that are associated with prenatal infection by the rubella virus. It is possible that the rubella virus infection during this critical stage of fetal development interferes with this maturation process. Similarly, patients with this syndrome may have a developmental defect involving this switch mechanism and preventing the generation of IgG and IgA(Schmicke *et al.* 1967). The alteration of normal defense mechanisms that permit persistent shedding of the virus is puzzling aspect of the rubella syndrome. For example the peripheral blood lymphocytes from rubella patients respond poorly to phytohemmaglutinin(Olsen *et al.* 1968) and this defect can be introduced in normal lymphocytes by infection with the rubella virus(Montgomery *et al.* 1967) and White *et al.* (1968) reported that transformation of lymphocytes from rubella patients by specific antigen was also impaired. In this respect, 1:44 positive IgM antibody titer in this patient is worth of mentioning. More interestingly, the lymph node finding showed focal small areas of necrosis, which is suggestive of virus infection. But we can not rule out the possibility of postnatal rubella infection and persistent rubella IgM antibody production due to altered immune response, which should be evaluated by follow up serology.

Another aspect which is especially puzzling in this case is the presence of aortic calcification and huge dilatation. His high blood pressure can be explained by the stenotic renal artery. Renin assay in serum was above the normal range (16.4ng/ml) and aldosterone was also elevated(440 pg/ml). We can speculate that stenotic renal artery resulted in activation of renin angiotensin system, which caused hypertension. Aortic calcification is hard to be explained. Thrombocytopenia, hemolytic ane-

mia, nephritis and arthritis, possibly representing manifestation of autoimmune process, have been reported (Goldmann *et al.* 1967). But in this case we could not find aortic involvement in the literature. But we can speculate the possibility that altered immune response provoked the aortitis and subsequently resulted in calcification.

REFERENCES

Goldman AS, Ritzmann SE, Houston EW, Sidewell S, Bratcher R, Lewn WC. Dysgammaglobulinemic antibody deficiency syndrome. J. Pediatr. 1967, 70:16-27

Krantman JH, Stiem ER, Stevens RH, Saxon RC. Abnormalities in B cell differentiation and T cell suppression in immunodeficiency with hyper-IgM. Pediat. Res. 1978, 12:482(abstract)

Montgomery JR. Viral inhibition of lymphocyte responses to phytohemmaglutinin. Science. 1967, 157:168-1070

Oldon GB. Abnormalities of in vitro lymphocyte response during rubella virus infections. J. Exp. Med. 1968, 128:44-68

Rosen FS, Kevy SV, Merler E, Janewy CA, Gitlin D. Recurrent bacterial infections and dysgammaglobulinemia: Deficiency of 7s gammaglobulins in the presence of elevated 19s gammaglobulins. Pediatrics 1961, 28:182-195

Schimike RN, Bolano C, Kirkpatrck CH. Immunologic deficiency in the congenital rubella syndrome. Amer. J. Dis. Child. 1969, 118:527-633

Stiem ER, Fudenberg HH. Clinical and immunologic features of dysgammaglobulinemia type 1: Report of a case diagnosed in the first year of life. Amer. J. Med. 1966, 40:805-815

White LR. Immune competence in congenital rubella: lymphocyte transformation, delayed hypersensitivity and response to vaccination. J. Pediatr. 1986, 73:229-234

=국문초록=

대동맥 석회화를 동반한 이상 감마글로부린 혈증

서울대학교 의과대학 소아과학교실, 병리학교실*, 임상병리학교실** 및 미생물학교실***

진동규 · 이환종 · 안효섭 · 최용 · 문형로 · 김철우* · 지제근* · 박명희** · 황응수***

이상 감마글로부린 혈증 1형은 면역 글로부린 G, A가 감소하거나 결핍되며, 면역 글로부린 M이 정상이거나 증가하는 질환으로서 반복되는 세균성 감염 및 자가 면역성 질환을 동반한다.

본 예는 4년 9개월된 남아로서 임파절 종창을 주소로 입원하여 골수 검사 및 임파조직 검사상 여포성 증식을 보였으며, 4년후 호흡곤란 및 두통을 주소로 재입원하여 상기한 면역 글로부린의 소견을 보이고 복부 X선 사진상 복부 대동맥의 석회화와 확장을 보였고 T 임파구 및 B 임파구 기능 검사상 과다 억제기능을 보인 예로서 보고하였다.