INTRODUCTION

Although the incidence of bacterial pneumonia has steadily decreased according to the improved public hygiene in the developed countries, Streptococcus pneumoniae is still one of the most common pathogens of childhood empyema (1). Transient hypogammaglobulinemia of infancy (THI) is originally defined as a physiological maturation defect of immunoglobulin G (IgG) production that occurs at 3-6 months of age and lasts until 18 to 36 months of age. We report here on a 22-month-old child with THI and IgA deficiency, who had massive pneumococcal empyema. Her depressed IgG level returned to normal within 6 months, but IgA level was still low at 6 yr of age. Although THI is an age-dependent and self-limiting disorder, severe infection that includes an atypical presentation of an infection may occur in some patients and this requires evaluation with immunologic study.

CASE REPORT

A 22-month-old girl was admitted to our hospital because of dyspnea and peripheral cyanosis for 2 days. She was born at full term and had been healthy until this event. She had no known history of severe infections and no familial history of immunodeficiency. Before admission, she had complained of cough with sputum for 2 weeks and she had visited private clinics 3 times. Fever was noticed for 2 days at the first visit to the clinic, since then she had remained afebrile. The weight, height and head circumference of the patient were within the normal percentile ranges for her age. Laboratory investigations revealed hemoglobin 14.9 g/dL, white blood cell count 14,000/μL (66% neutrophils and 30% lymphocytes), platelet count 123,000/μL, erythrocyte sedimentation rate at 1 hr 2 mm/hr and C-reactive protein 0.1 mg/dL. The blood chemistry analysis was non-specific except elevated alkaline phosphatase 685 IU/L (96-254 IU/L) and lactate dehydrogenase (LDH) 823 IU/L (145-420 IU/L). The serum complement levels were C3 61.4 mg/dL (77-195 mg/dL), and C4 10.0 g/dL (7-40 mg/dL). The blood chemistry analysis was non-specific except elevated alkaline phosphatase 685 IU/L (96-254 IU/L) and lactate dehydrogenase (LDH) 823 IU/L (145-420 IU/L). The serum complement levels were C3 61.4 mg/dL (77-195 mg/dL), and C4 10.0 g/dL (7-40 mg/dL).

A chest computed tomography (CT) performed on admission day showed massive pleural effusion with a totally collapsed left lung, and the heart was shifted to the right side (Fig. 1). The values of immunoglobulins on the 14th admission day were IgG 336 mg/dL (reference level for age: 345-1,236 mg/dL), IgA <13 mg/dL (14-159 mg/dL), IgM 87.6 mg/dL (43-207 mg/dL) and IgE 31 IU/mL (0-170 IU/mL). Although all the values of IgG subclasses were low, there was no IgG subclass that was not detected. Isohemagglutinin and the antibodies from vaccination (anti-diphtheria IgG, anti-tetanus IgG and anti-polio virus IgGs) were all detected. The lymphocyte subset tests showed that the pan-T cells...
were 51.6% (28-77%), the CD4+ cells 25.3% (32-68%),
the CD8+ cells 23.6% (10-36%) and the B cells 36.5% (10-
20%). The nitroblue tetrazolium test was negative. The degree
of T cell proliferation to mitogens (phytohemagglutinin and
anti-CD3/anti-CD 28 monoclonal antibodies) was compa-
rable to that of the age-matched control.

On the second day of hospitalization, a chest tube was
inserted to the pleural cavity and ~300 mL of milky colored
fluid was evacuated. The pleural fluid analysis revealed an
exudate with subsequent heavy growth of *S. pneumoniae*;
the organism was resistant to penicillin, but sensitive to ceftri-
axone. The clinical course of the patient treated with the
chest tube drainage and an antibiotic regimen (ceftriaxone)
was uneventful and there was no residual lesion on the chest
radiograph taken 6 months later. The patient did not receive
intravenous immunoglobulin therapy during hospitalization or
subsequent supplementary therapy for hypogammaglob-
ulinemia. After 1 yr, the low levels of IgG and C3 and the
ratio of CD4+ T cells were recovered to within the normal
range for her age, but her IgA level did not recover (Table 1).

### DISCUSSION

The immune system of early childhood is not fully ma-
tured compared to adults, and some immune functions may
mature during childhood. The phenotype of some infectious
diseases such as hepatitis A is age-dependent, and most chil-
dren under 5 yr of age are largely asymptomatic or innocu-
ous without jaundice when they are affected by hepatitis A
virus (6). Kawasaki disease is an acute febrile systemic vas-
culitis of an unknown etiology, but it may be an immune-
mediated disease that manifests after an infection by un-
known pathogens (7). This disease has a strict age predilec-
tion between 6 months and 4 yr of age. In addition, other early childhood immune-mediated disorders that have a strict age
restrictions with a self-limited clinical nature are known;
transient erythoblastopenia of childhood (TEC) (8), autoim-
une neutropenia of infancy (ANI) (9), and childhood im-
une thrombocytopenic purpura (ITP) (10). All these find-
ings indicate that the maturing immune system in early
childhood (< 5 yr of age) may be involved in the phenotype
of infectious and immune-mediated disorders. THI also occurs
mainly at 3-6 months of age and it lasts until 18 to 36 months
of age with self-limiting recovery. Thus, it may be regarded
as one of the disease category that reflects immunologic im-
maturity during early childhood. The pathogenesis of THI
remains unknown, although delayed functional maturation
of B cells, a numerical reduction of helper T cells (also sug-
gested in our case), and cytokine imbalance have been postu-
lated (2-5, 11, 12). Most of the children with TEC, ANI or
ITP are proposed to experience a variety of infections, and
especially those of a viral origin before presentation of illness.
It is postulated that THI may also be associated with an in-
fec tion and the subsequent immune perturbation is respon-
sible for the pathogenesis of THI.

Neutrophils and other phagocytes are the first defense line
against extracellular bacterial pathogens, and humoral immu-
nity (antibodies) has a crucial role for phagocytosis against
encapsulated bacteria such as *S. pneumoniae* and *H. influenzae*.
Thus, the patients with humoral immunodeficiencies such as
X-linked agammaglobulinemia (XLA) and common vari-
able immunodeficiency (CVID) mainly complain of recur-
rent infections from such bacteria (13).

A majority of children with THI are detected by clinical
manifestations like recurrent upper respiratory infections, but
they have few severe infections during the follow-up period
(2-5). Some children with THI experience severe or life-threat-
ening infections such as sepsis or severe pneumonia, like hap-
pened in our case (14-16). Since the patients with THI are
believed to have a normal capacity to produce specific anti-
bodies, in contrast to XLA and CVID patients, the low level
of IgG alone may not be responsible for a severe infection

| Age (months) | Immunoglobulin G (mg/dL) | Immunoglobulin A (mg/dL) |
|-------------|--------------------------|--------------------------|
| 22          | 336                      | <13                      |
| 24          | 405                      | <13                      |
| 28          | 491                      | <13                      |
| 34          | 808                      | 26                       |
| 60          | 723                      | 27                       |
| 68          | 768                      | 24                       |

Table 1. Serial immunoglobulin levels of our patient

Fig. 1. A chest CT performed on admission day shows massive pleural effusion with total collapse of left lung. The mediastinum
shifts to right side.
with encapsulated bacteria. Our patient was also noted to have an intact humoral immunity and a normal T cell proliferation response with a decreased CD4+ T cell count. The low levels of IgG, C3 and CD4+ T cells were recovered within 6-12 months. Thus, other transient immune disturbances concerned with phagocytosis or other immune function may manifest severe infections in some of the patients with THI, including our case, although we did not perform extended immunologic studies at presentation.

Previous studies have indicated that a subgroup of THI patients had a persistent low value of IgG beyond >4 yr of age and this was commonly associated with low IgA values (IgA immunodeficiency) or dysgammaglobulinemia (2-5, 14). These findings suggest that THI may consist of a heterogeneous group of immunodeficiencies and THI may have the possibility of an early manifestation of a primary immunodeficiency such as CVID, although there are few reports on the association between THI and primary immunodeficiency.

Although THI is an age-dependent and self-limiting disorder, severe infections may occur, including atypical presentation of infections that need immunologic study. Long-term follow-up of the clinical condition of these patients and their immunologic status are necessary to rule out primary immunodeficiency disorders.

REFERENCES

1. Shen YH, Hwang KP, Niu CK. Complicated parapneumonic effusion and empyema in children. J Microbiol Immunol Infect 2006; 39: 483-8.
2. McGeady SJ. Transient hypogammaglobulinemia of infancy; need to reconsider name and definition. J Pediatr 1987; 110: 47-50.
3. Kilic SS, Tezcan I, Sanal O, Metin A, Essoy F. Transient hypogammaglobulinemia of infancy: clinical and immunological features of 40 new cases. Pediatr Int 2000; 42: 647-50.
4. Kidon MI, Handzel ZT, Schwartz R, Altboum I, Stein M, Zan-Bar I. Symptomatic hypogammaglobulinemia in infancy and childhood: clinical outcome and in vitro immune responses. BMC Fam Pract 2004; 5: 23.
5. Whelan MA, Hwan WH, Beausoleil J, Hauck WW, MaGeady SJ. Infants presenting with recurrent infections and low immunoglobulins: characteristics and analysis of normalization. J Clin Immunol 2006; 26: 7-11.
6. Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. Vaccine 1992; 10 (Suppl 1): S15-7.
7. Lee KY, Han JW, Lee JS. Kawasaki disease may be a hyperimmune reaction of genetically susceptible children to variants of normal environmental flora. Med Hypotheses 2007; 69: 642-51.
8. Cherick I, Karayalcin G, Lanzkowsky P. Transient erythroblastopenia of childhood. Prospective study of fifty patients. Am J Pediatr Hematol Oncol 1994; 16: 320-4.
9. Bux J, Behrens G, Jaeger G, Welte K. Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. Blood 1998; 91: 181-6.
10. Blanchette VS, Carcao M. Childhood acute immune thrombocytopenic purpura: 20 years later. Semin Thromb Hemost 2003; 29: 605-17.
11. Siegel RL, Issekutz T, Schwaber J, Rosen FS, Geha RS. Deficiency of T helper cells in transient hypogammaglobulinemia of infancy. N Engl J Med 1981; 305: 1307-13.
12. Kowalczyk D, Mytar B, Zembala M. Cytokine production in transient hypogammaglobulinemia and isolated IgA deficiency. J Allergy Clin Immunol 1997; 100: 556-62.
13. Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 2002; 109: 581-91.
14. Benderly A, Pollack S, Etzioni A. Transient hypogammaglobulinemia of infancy with severe bacterial infections and persistent IgA deficiency. Isr J Med Sci 1986; 22: 393-6.
15. Smart JM, Kemp AS, Armstrong DS. Pneumocystitis carinii pneumonia in an infant with transient hypogammaglobulinemia of infancy. Arch Dis Child 2002; 87: 449-50.
16. Hsueh KC, Chiu HH, Lin HC, Hsu CH, Tsai FJ. Transient hypogammaglobulinemia of infancy presenting as Staphylococcus aureus sepsis with deep neck infection. J Microbiol Immunol Infect 2005; 38: 141-4.