Occurrence of Leukemia and Lymphoma in Patients with Agammaglobulinemia

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The recent finding of malignant lymphoma and acute lymphatic leukemia in patients with congenital agammaglobulinemia carries implications that make it seem important to describe the following case reports.

Case #1*

This white male child was normal until the age of 6 months when he began to have recurrent upper respiratory and gastrointestinal infections. When he was 18 months old, he developed poliomyelitis and was left with some residual weakness of the legs. A few months later a diagnosis of dermatomyositis was made on the basis of generalized muscle weakness, induration of the skin, and chronic inflammatory changes in skin and muscle biopsy tissue. The child continued to have recurrent bouts of bacterial infection, including episodes of pharyngitis, otitis media, pneumonia, and meningitis.

Serum electrophoresis was done for the first time when the patient was 3, and revealed absence of the gamma globulin fraction. Blood isoagglutinins were absent, zinc turbidity was 0.1 unit, and the gamma globulin concentration by a sensitive immunochromat method was 16 mg. per cent. These studies and the history of repeated bacterial infection established this as a case of congenital agammaglobulinemia. At about this same time, hepatomegaly and large, matted axillary and inguinal lymph nodes were noted. Studies of the bone marrow and peripheral blood revealed normal findings, except for toxic granulation of the neutrophil series. A lymph node biopsy showed only benign hyperplasia.

After the child was started on gamma globulin replacement therapy (0.6 cc./Kg./month), the number of infections decreased. However, the dermatomyositis progressed, with increased induration of skin and muscles and development of contractures. At the age of 4, he had several generalized convulsions. Skull x-rays and a pneumoencephalogram showed no abnormalities, and the seizures did not recur. Steroid therapy was instituted for a period of several months without significant change in the dermatomyositis. During this period the patient suffered a fracture of the left femur that occurred without significant trauma.

At the age of 4 years, 8 months, he suffered a short febrile illness and died in respiratory distress. Figure 1 is a photograph of this child during his last illness. It shows the wasting of the muscles, enlarged abdomen, tight shiny skin, and contractures of the hips, knees, and ankles. There was marked growth failure; when he died, the child weighed only 35 pounds and was 35 inches tall.

The autopsy revealed pulmonary congestion and edema, as well as ascites (about 600 cc. of straw-colored fluid in the peritoneal sac). The liver was enlarged, weighing 800 Gm., as were the kidneys: 160 and 170 Gm. The spleen was normal in size. The bone marrow was normal. Microscopic examination of liver tissue revealed extensive mononuclear cell infiltration of the portal triads with some extension into the sinusoids. These cells had large immature nuclei with only a small cytoplasmic rim (fig. 2). The kidneys showed...
Fig. 1.—Case #1, a 4½ year old boy with dermatomyositis, agammaglobulinemia and malignant lymphoma. Note the tight skin and contractures of the ankles, knees and hips.

extensive infiltration of the same type of immature cell into the interstitial tissue between the tubules, and the architecture of the mesenteric lymph nodes was destroyed by the cellular infiltrate. Sections of spleen showed congestion of the sinusoids and small follicles. A postmortem diagnosis of malignant lymphoma was made on the basis of the findings in the lymph nodes, liver and kidneys.

This case, then, represents a child with congenital agammaglobulinemia who developed the typical clinical and pathologic picture of dermatomyositis at 2 years of age, and died with "malignant lymphoma" at 4 years, 8 months.

Case #2

This white male child was the brother of a boy with congenital agammaglobulinemia, and was followed from birth, with frequent determinations of the serum gamma globulin level. A diagnosis of agammaglobulinemia was established by the age of 6 months. Figure 3 graphs this child's gamma globulin levels. He was never given gamma globulin, but received a daily dosage of 125 mg. of tetracycline hydrochloride. The patient grew well and had no unusual difficulty with infections.

When he was 11 months old, he was immunized with poliomyelitis, mumps, diphtheria-pertussis-tetanus, and typhoid-paratyphoid vaccines. Efforts to detect antibody against the polio, mumps, typhoid, and diphtheria antigens were unavailing. At the age of 12 months, oral penicillin (250,000 units twice a day) was substituted for the tetracycline. At 21 months, the child had chicken pox and recovered without incident.

Because the patient's serum gamma globulin rose from 10 mg. per cent at age 1 year to 160 mg. per cent at age 3 years, typhoid and mumps vaccines were again administered, and again the patient failed to respond with production of detectable amounts of antibody. Immunoelectrophoresis was performed several times and each time revealed very low levels of gamma globulin and complete absence of the immunoglobulins beta2A and beta2M. He continued to grow and develop normally, and had no problem with infections.

When he was 3 years, 8 months old, he sustained second-degree, hot water burns to parts of the right leg and left arm. He was given 10,000 units of tetanus antitoxin and 12 cc. of gamma globulin. The burns healed, but beginning about 3 weeks after the injection of foreign serum and for the next 4 months, the patient had recurrent transient urticaria. Four months after the burn, he had sudden onset of fever and lymphadenitis. Chest x-ray revealed a large anterior mediastinal mass, apparently massive enlargement of the thymus (fig. 4). The white blood count was 240,000 per cu. mm., with 69 per cent lymphoblasts, 13 per cent neutrophils and 18 per cent lymphocytes. Examination of the bone marrow confirmed the diagnosis of acute lymphocytic leukemia.
The patient was given 6-mercaptopurine and responded with complete disappearance of the mediastinal mass and lymphadenopathy within 2 weeks (fig. 4). The peripheral blood was completely normal after 3 weeks of therapy. This remission lasted for 3 weeks, when lymphadenopathy reappeared without hematologic exacerbation. The patient was then treated with cortisone and the enlarged nodes receded. Cortisone was stopped and 6-MP continued. He remained well for an additional month, and then had recurrence of the mediastinal mass. Amethopterin therapy was instituted, and 6-MP was stopped. The
mass continued to grow, however, and a left pleural effusion developed. He developed severe gastrointestinal toxicity after 12 days on amethopterin, and administration of the drug was discontinued. Cortisone and x-ray therapy to the chest failed to halt progress of the disease, and the patient died 4½ months after onset of the leukemia.

Autopsy revealed generalized peripheral lymph node enlargement. The tumor in the anterior mediastinum filled most of the left thoracic cavity. The thymus could not be identified as an entity separate from the anterior mediastinal mass. There was 400 cc. of blood in the left thoracic cavity and the left lung was atelectatic. The right lung was normal. The liver was enlarged to 810 Gm. The kidneys were enlarged and anomalous, with double pelvices and ureters on both sides; they weighed 106 and 205 Gm. The normal-sized spleen weighed 53 Gm. Microscopic studies showed leukemic infiltration of the liver, kidneys, spleen, lymph nodes, and anterior mediastinum (fig. 5).

In summary, this was a patient with established congenital agammaglobulinemia, probably of the sex-linked recessive form, who was well until 4 years of age when he developed acute lymphatic leukemia.

**DISCUSSION**

The presence of three diseases in Case #1 makes interpretation difficult but of considerable interest. Dermatomyositis has previously been reported in a patient with agammaglobulinemia and in patients with malignant disease.

The association of dermatomyositis with both carcinoma and lymphoma is well established for adults over 40 years of age. The only reported case of dermatomyositis associated with tumors of any kind in the pediatric age group was that of an 11-year-old girl who had both dermatomyositis and a
chromaphobe adenoma of the pituitary. In adults it appears that dermatomyositis may be caused by or be associated in some way with a hidden malignant lesion, for in most cases the diagnosis of dermatomyositis has preceded the diagnosis of malignancy and often, as in our case, the malignancy goes undetected until postmortem examination. It is possible that in our patient the lymphoma was present at age 2 when dermatomyositis was diagnosed. Against this possibility is the lymph node biopsy at age 3 that did not show evidence of lymphoma and also the fact that malignant lymphoma in this age group is a rapidly progressive disease. However, if the lymphoma was actually present at age 2, the question of whether the agammaglobulinemia was secondary to the lymphoma must be raised. This again seems unlikely to us because although the diagnosis of agammaglobulinemia was not established until age 3, the patient had already shown symptoms of decreased resistance to infection by age 6 months, just when patients with congenital agammaglobulinemia became symptomatic because of loss of passive protection.

In our second case, the diagnosis of agammaglobulinemia was established by age 6 months and evidence of leukemia did not appear until age 4 years. The natural history of acute lymphatic leukemia is such that it seems reasonable to assume that the agammaglobulinemia preceded the leukemia in this patient. Further, the patient's brother has classical agammaglobulinemia, presumably of the sex-linked recessive type which has been diagnosed for 10 years now with no sign of associated lymphomatous disease.

Approximately 30 per cent of patients with malignant lymphoma have hypogammaglobulinemia (10-13) and a few patients (13-15) have had serum gamma globulin levels low enough to be considered extremely hypogammaglobulinemic or agammaglobulinemic. In these cases, the hypogammaglobulinemia has been considered secondary to the lymphoma on the assumption that replacement of normal lymphoid tissue by malignant cells reduced the numbers of gamma globulin producing cells. There have, however, been two recent case reports of patients who developed malignant lymphoma long after
Fig. 5.—Case #2. A. Peripheral blood showing lymphoblasts. B. Peripheral blood revealing a reticulum cell, three lymphoblasts, two lymphocytes and one neutrophil. C. Autopsy specimen of liver showing periportal infiltration of lymphoid cells. This type of infiltration is typical of that seen in acute lymphoblastic leukemia. D. Autopsy specimen of kidney revealing interstitial infiltration of leukemic cells.

a diagnosis of hypogammaglobulinemia had been established. Fudenberg and Solomon\textsuperscript{16} described a man who developed symptoms of acquired hypogammaglobulinemia 18 years before his death; hypogammaglobulinemia was established by electrophoresis 2 years before death; and a malignant lymphoma of the spleen was found at autopsy. This would certainly be an unusual natural course of a lymphomatous process and it seems to us likely that the agammaglobulinemia really did precede the development of the malignant
Lymphoma and was not a secondary consequence of the malignant disease. The second case, a CPC in the American Journal of Medicine, was a patient who was found to be hypogammaglobulinemic at age 12 and who died of reticulum cell sarcoma at 20. In both of these instances, and in the two patients described in this report, we feel that the evidence is good that agammaglobulinemia preceded the development of malignant lymphoma.

We also feel strongly that our two cases of malignant lymphoma in agammaglobulinemic children constitute a greater-than-chance occurrence of this disease. In our area, the risk of leukemia in the pediatric group of highest incidence, birth to 4 years of age, is one in 20,000 risk-years, and the risk of other forms of lymphoma in this age group is even less. Therefore, the occurrence of two patients with these closely related diseases in the population of 24 children with congenital agammaglobulinemia almost certainly represents a true increase in the incidence of malignant lymphoma in this patient group.

The finding that these patients with an immunologic deficiency have increased susceptibility to malignant lymphoma is exciting, and several possible explanations for this relationship immediately come to mind:

1) Malignancy may, in some cases, be due to failure of the body to destroy abnormal mutant cells. In fact, nearly 10 years ago, Thomas predicted that agammaglobulinemic patients would develop cancer on the basis of failure to recognize and destroy mutant cells as efficiently as the immunologically normal person. In this regard, the occurrence of other tumors such as fibromata, osteochondromata and gastric carcinoma in patients with hypogammaglobulinemia may be meaningful.

2) Malignancy may be the result of a virus infection. In recent years, more and more evidence has indicated the importance of viruses in the etiology of tumors and it now appears that identification of human tumor viruses is a certainty. If human leukemia and malignant lymphoma are indeed caused by an infecting agent, one might anticipate that patients with a defect in their ability to resist infection might show increased susceptibility to these diseases. Although it is true that agammaglobulinemic patients are able to acquire immunity to some viral infections, a defect in protective mechanisms against at least one viral disease, serum hepatitis, has been documented.

3) An abnormality of thymic function may be responsible for both agammaglobulinemia and the propensity toward development of lymphoma and leukemia. Recent evidence indicates that the thymus in mammals are key organs in the development of full immunologic capacity. It is also known that the thymus is essential to the full expression of leukemia in certain inbred strains of mice. It even seems probable that mouse leukemia regularly originates in the thymus. Further, thymus abnormalities (benign thymoma) are known to occur far too frequently among patients with acquired agammaglobulinemia. Therefore, it seems possible that the association of agammaglobulinemia and lymphoma is the result of a thymic abnormality. This concept seems particularly attractive in Case #2 in this report in whom the leukemia presented as a massive enlargement of the thymus.
4) Perhaps the increased incidence of lymphoma in these patients is not secondary to the immunologic defect, but rather another manifestation of basically abnormal mesenchymal tissues. Agammaglobulinemic patients as a group have an unusually high incidence of mesenchymal disease and some recent family studies have indicated that this is often true of their close relatives as well.\textsuperscript{36-37} Further, many patients with acquired agammaglobulinemia have hypertrophy of the lymphoid tissue; in fact, a pathologic diagnosis of benign follicular lymphoblastoma is relatively common in this group.\textsuperscript{15,36-40}

5) Another possibility which must be considered is that in some way antigenic stimulation, perhaps responsible for or associated with the dermatomyositis in Case \#1 and with the injection of horse serum in Case \#2, led to malignant transformation of the lymphoid tissue when the appropriate response of the lymphoid tissue could not occur in the agammaglobulinemic children.

It is possible that one or more of these mechanisms is responsible for the development of malignancy of the lymphoid tissues in the agammaglobulinemic patients. It may be that the factors responsible for lymphoma in the patients with acquired agammaglobulinemia differ from those responsible for the disease in the congenital agammaglobulinemia group, but it is attractive to search for a single mechanism which may account for the high incidence of the simultaneous occurrences of these malignancies of the lymphoid tissue and the immunologic deficiency in these several circumstances.

We hope that these case reports will stimulate a careful appraisal in other quarters of the association of malignancy and the immunologic deficiency diseases.

**Summary**

1) Two case reports of children with congenital agammaglobulinemia who later developed malignant lymphoma are presented.

2) Two additional cases of malignant lymphoma developing in adult patients with hypogammaglobulinemia are reviewed.

3) The occurrence of diseases of this group among patients with this immunologic defect appears to be a greater-than-chance association. Possible reasons for the association are discussed.

**Summario in Interlingua**

1. Es reportate le casos de duo juveniles con congenite agammaglobulinemia qui subsequentemente disveloppava lymphoma maligne.

2. Es revistate duo casos additional in que lymphoma maligne se disveloppava in patientes adulte qui etiam habeva hypogammaglobulinemia.

3. Le occurrentia de morbos de iste gruppo in patientes con le mentionate defecto immunologic pare haber un frequentia plus que aleatori. Possibile rationes pro le association es discutite.

**References**


29. Thomas, L.: Personal communication.


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