Lymphangioma refers to the local proliferation of well-differentiated lymphatic tissue. Generalized lymphangiomatosis is rare. We report a previously healthy 8-month-old infant who suffered from tachypnea with mild fever for 2 weeks. Imaging studies revealed a well-defined, large mass occupying the mediastinum, which presented as cardiomegaly. The disseminated mass extended to the thymus, lung, and spleen. Lymphangiomatosis was diagnosed by biopsy. Drainage of the pericardial fluid and total parental nutrition did not result in improvement of chylopericardium. Secondary hypogammaglobulinemia and septic shock developed sequentially. Surgical removal of the mediastinal mass and spleen were performed. Daily subcutaneous injection of interferon (IFN) alpha-2b was then given for 3 months. No recurrence was noted during 2 years of follow-up. IFN alpha-2b may be considered as an alternative for the treatment of generalized lymphangiomatosis. [J Formos Med Assoc 2007;106(3 Suppl):S10–S14]

Key Words: chylopericardium, generalized lymphangiomatosis, interferon alpha-2b

Lymphangioma refers to the local proliferation of well-differentiated lymphatic tissue, which may involve the head and neck regions, axilla, lungs, pleura, bones, liver, spleen, and other regions, except for the central nervous system. Generalized lymphangiomatosis is a rare disease characterized by widespread abnormality of the lymphatic system. Here, we report a female infant with generalized lymphangiomatosis presenting with chylopericardium and intractable chylothorax.

Case Report

An 8-month-old, well-nourished female infant suffered from nonproductive cough for 2 weeks. Mild fever (body temperature, 38°C) and tachypnea developed 1 day before admission. Chest roentgenogram showed cardiomegaly (water-bottle appearance) with a widening mediastinum and increased infiltration over bilateral lung fields (Figure 1A). Hemogram at admission was normal except for thrombocytopenia (platelet count, 87,000/μL). Two-dimensional echocardiography demonstrated a large fluid-filled pericardial space without cardiac dysfunction; 58 mL of serosanguineous fluid was aspirated via pericardiocentesis. Analysis of the aspirate showed chylous fluid (triglycerides, 134 mg/dL) without evidence of infection or malignancy (acid-fast stain for three sets and TB culture all negative; bacterial culture negative; viral isolation negative; cytology revealed only small lymphoid cells). The pericardial effusion reaccumulated 4 hours later, so a pericardial
window was created via pericardiectomy to prevent tamponade. Biopsy of the pericardium showed only fibrosis. Computed tomography of the chest and abdomen showed an anterior mediastinal mass, pericardial effusion, and splenomegaly infiltrated by hypoechoic nodules (Figure 1B and C).

Massive, bloody pericardial effusion was drained daily (200–640 mL/day). Complicating factors included bilateral lower leg edema and body weight gain (2 kg in 4 days) due to hypoalbuminemia and hypoglobulinemia (albumin 2.5 and globulin 1.5 g/dL). Intravenous immunoglobulin (IVIG, 1 g/kg/day for 1 day) and albumin (1 g/kg/day for 2 days) were administered as adjuvant treatment. Severe hypogammaglobulinemia (IgG, 85.1; IgA, 25.5; IgM, 66.7; IgE, 8.8 mg/dL) was found 4 days after hospitalization. Exploratory thoracotomy was performed to evaluate the anterior mediastinal mass, and left parietal pleurectomy was also performed during the same procedure in an attempt to control the chylothorax. Then, the anterior mediastinal tumor was excised in its entirety. This soft tumor had an inverted T shape, was $7 \times 5 \times 1$ cm in size and was located in front of and adherent to the upper pericardium and the great vessels, encroaching on the brachiocephalic vein. It was easily peeled off from the pericardium. Multiple lymphatic channels were noted on the tumor. The pericardium was partially excised in order to create a pericardiopleural window. Microscopic examination of the resected thymic tumor revealed numerous irregularly dilated vascular spaces containing lymphatic fluid in the thymic tissue (Figure 2), leading to the diagnosis of thymic lymphangioma. Persistent chest tube drainage was required and total parenteral nutrition (TPN) and repeated component therapy of albumin and IVIG were given.

Enterobacter cloacae bacteremia with septic shock and pulmonary hemorrhage developed 3 weeks after the previous operation. Respiratory failure with complete whiteout of the left lung field was found and the patient was therefore intubated. A disseminated intravascular coagulation laboratory profile with thrombocytopenia (platelets, 21,000/dL) and anemia (hemoglobin, 5.8 g/dL) was found despite
component therapy. Rapidly progressive hepatosplenomegaly (liver, 9 cm; spleen, >11 cm palpable below the right costal margin) ensued. Due to chest tube drainage dysfunction and aggravation of the consumptive coagulopathy with splenomegaly, laparotomy was performed with splenectomy, left thoracotomy, and biopsy of lung. Immunohistochemical studies demonstrated focal, weak factor-VIII antigen staining of the cells lining the vascular channels of the spleen and lung. Pathology confirmed lymphangiomatosis involving the thymus, spleen, and lung. Serial imaging studies were characteristic of generalized lymphangiomatosis involving the neck, axilla, and the pericardium. The postoperative course was uneventful, and the coagulopathy with thrombocytopenia resolved following splenectomy. TPN was given with a low-fat, medium-chain triglyceride (MCT) diet after extubation. Amoxicillin for postsplenectomy chemoprophylaxis and a 3-month course of daily subcutaneous injections of interferon (IFN) alpha-2b at 3 million units/m² were given. There was no recurrence during follow-up for 2 years by serial imaging studies. The only side effect was mild fever during the initial 3 days of treatment.

Discussion

Lymphangiomas are congenital malformations of the lymphatic system that constitute 5.6% of all benign tumors in infancy and childhood. They grow very slowly and usually localize to one organ, but occasionally involve several organs. According to Noonan’s classification, generalized lymphangiomatosis is a subgroup of lymphangiectasia associated with diffuse lymphatic proliferation, with a particular pattern of visceral involvement and a progressive course. Factor VIII-related antigen and CD31 are the most reliable markers for identifying endothelial cells lining the lymphatic spaces. Clinical manifestations depend on the organ involved, and respiratory symptoms are often the initial manifestation. The prognosis is usually poor in patients with lung involvement.

The most difficult issues in managing patients with lymphangiomas are intractable pleural effusion and how to treat generalized lymphangiomatosis. Reported interventions for chylopericardium include pericardiocentesis, the creation of a pericardial window, pericardiectomy, ligation of the thoracic duct just above the diaphragm, and the resection of pathologic structures (e.g. tumors).
Ligation of the thoracic duct results in a good prognosis; lymph will travel via an anastomosis with the right lymphatic duct and by lymphaticovenous communications with the azygos vein. Regarding chylothorax, current treatment is palliative and involves drainage of the effusion when there is significant respiratory distress. If this fails to produce spontaneous resolution of the effusion, aggressive treatments such as surgical intervention and tetracycline pleurodesis are necessary to avoid the complications of poor nutrition, hypogammaglobulinemia, and lymphopenia under persistent drainage of lymph, as well as to improve the quality of life. Moreover, a low-fat MCT diet can also be beneficial since it reduces the rate of chyle formation. Regarding therapeutic modalities for lymphangiomas, complete surgical excision is the treatment of choice because lymphangiomas rarely resolve spontaneously. However, incomplete resections are common and there is a high rate of recurrence. Several nonsurgical interventions have been proposed for patients with unresectable lymphangiomas, including percutaneous sclerotherapy (steroid, hypertonic saline, ethanol, bleomycin, and OK-432 [Picibanil]), systemic corticosteroids, radiation therapy, and chemotherapy such as cyclophosphamide. However, the side effects of these modalities make them unsuitable for most patients. Multiple organ involvement makes percutaneous sclerotherapy impossible. The long-term sequelae of systemic corticosteroids and radiotherapy in children are well known. Chemotherapeutic agents such as cyclophosphamide have shown some promising effects in slowing or stopping the growth rate of most lymphangiomas, but the potential side effects are significant and include bone marrow suppression, impaired liver function, hemorrhagic cystitis, and late-onset malignancy.

Disseminated lymphangiomatosis may be a proliferative disorder and it is not surprising that IFN alpha plays a role in the treatment of this disease. This cytokine has emerged as an important regulator of cell growth and differentiation. Tazelaar et al reported the use of IFN in three patients with diffuse pulmonary lymphangiomatosis. One of these patients was stable after 20 months of treatment with IFN alpha, one died of massive hemoptysis 18 months after initiating IFN alpha treatment, and one did not have sufficient follow-up. Margraf reported a 10-year-old boy with thoracic lymphangiomatosis with unsuccessful use of IFN alpha in an attempt to abate severe respiratory failure. Reinhardt et al reported two patients with lymphangiomatosis successfully treated by IFN alpha. Laverdiere et al reported a 3-year-old boy with generalized lymphangiomatosis involving lung, ribcage, and spleen. He showed significant clinical and radiologic improvement after 28 months of IFN alpha-2b treatment without significant toxicity. Whether this treatment is successful may depend on the disease severity, the general condition, and the dose and duration of IFN alpha treatment.

Our patient had the unusual initial presentation of cardiomegaly and extensive involvement including the thymus, spleen, and lung, and highly probable neck, axilla, and pericardium involvement. Conservative treatment including drainage of the pericardial and pleural fluid and lessening of lymph production via TPN supplement was ineffective. Complete surgical excision of the thymus and the spleen were performed and adjuvant IFN alpha-2b treatment was given for disseminated involvement. Clinical and radiologic improvement was noted after 3 months of treatment with IFN alpha and no significant side effects occurred except for a mild fever during the initial 3 days of treatment. Her condition was stable for 2 years following the completion of IFN alpha treatment.

References


