

*Clinical pearls***Long-term follow-up of patients with primary immunodeficiencies**

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As an example of the need for long-term follow-up by specialty health care to adequately manage immunodeficient patients, we report the case of a patient with Wiskott-Aldrich syndrome who was lost to follow-up for 4 years to the immunology clinic and came back with a neck mass that was diagnosed as B-cell lymphoma. Patients with immunodeficiency are at high risk for the development of malignancy and autoimmune diseases and should be evaluated by a trained specialist with a frequency of not less than every 6 months. (*J Allergy Clin Immunol* 2007;■■■:■■■-■■■.)

Key words: Primary immunodeficiency, Wiskott-Aldrich syndrome, B-cell lymphoma

More than 150 primary immunodeficiency (PID) syndromes have been described to date, encompassing a range of defects in the immune system and a wide spectrum of clinical severity. Many of these conditions, such as severe combined immunodeficiency, are fatal without curative treatment. Patients with severe combined immunodeficiency can receive hematopoietic stem cell transplantation and acquire a functional immune system; however, at least a third of patients remain dependent on monthly immunoglobulin infusions. Other patients with moderately severe PIDs require chronic therapy to prolong life expectancy; for example, patients with combined variable immunodeficiency (CVID) survive over decades with administration of immunoglobulin replacement and antibiotic prophylaxis. With the economic constraints of insufficient medical insurance coverage and the increased availability of medical treatment and procedures

Abbreviations used

CVID: Combined variable immunodeficiency
PID: Primary immunodeficiency
WAS: Wiskott-Aldrich syndrome

performed at home, such as the administration of subcutaneous immunoglobulins, some patients and their physicians might elect to reduce the frequency of regular visits for physician evaluation. To discuss the importance of the long-term follow up of patients with PID, we present the case of a patient with Wiskott-Aldrich syndrome (WAS) who was lost to specialty care follow-up for 4 years and returned with a large neck mass.

CASE REPORT

A 21-year-old man with WAS, characterized by thrombocytopenia with low platelet volume, eczema, and immunodeficiency, was seen in our clinic because of a neck mass. During childhood, he had several upper respiratory tract infections and received platelet transfusions 3 times. He had been hospitalized for a hernia repair, varicella infection, and a thigh abscess. Cervical and submental lymphadenopathy had been noted since 3 years of age, which was most prominent in the anterior right cervical chain with a fluctuating size and a maximum diameter of 6 cm without pain, tenderness, or any problems caused by the mass size, such as swallowing difficulty. Histopathologic studies of these lymph nodes on 2 occasions (last biopsy at age 8 years) were reported as “reactive lymph nodes,” and therefore no other intervention other than close follow-up was recommended. A detailed visit interval history, a complete physical examination, and immunologic testing (blood cell count and differential, lymphocyte phenotype, and mitogen and antigen proliferative response) were performed every 6 months at the Hematology and the Allergy and Immunology Clinics at Texas Children’s Hospital until the patient was 17 years old. At that time, his cervical adenopathy was still noticeable, but his clinical course was stable. He had ongoing eczema and thrombocytopenia but had no bleeding or bruising. His medications were cotrimoxazol as prophylaxis for bacterial infections and for *Pneumocystis jiroveci* pneumonia and topical corticosteroids for eczema.

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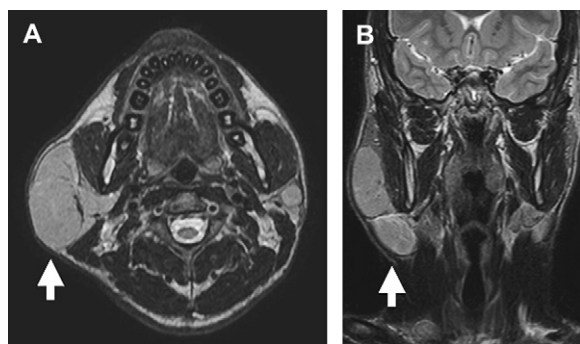


FIG 1. An axial section (A) and a coronal section (B) of a T2-weighted magnetic resonance image of the neck shows a large mass (arrows) in the right aspect of the neck that measures 6.5 cm in diameter and is 9.5 cm long, with a density similar to that of lymph node tissue.

The patient elected to stop attending the specialty clinics for the next 4 years. Six months before the current visit, the patient noted a progressive increase in the size of the cervical mass but no additional symptoms. Because the patient and his family had been through several episodes of cervical adenitis, he did not seek medical advice until 5 months later, when he was evaluated by his primary physician and received empiric antibiotic treatment for probable adenitis that did not result in a therapeutic response. He was referred to the allergy and immunology clinic, where he was found to have a right neck mass extending from the right cheek to the right lower end of the neck (12 cm in length and 8 cm wide) that was not painful, not mobile, and of a rubbery consistency. A computed tomographic scan of the neck showed a large mass inferior to the parotid gland (Fig 1). A positron emission tomographic study demonstrated hypermetabolic activity in the neck mass and in a left axillary lymph node. A biopsy was performed, and pathology studies supported the diagnosis of diffuse large B-cell lymphoma, stage 2. Tissue staining for EBV EBER protein was not characteristic for EBV-driven lymphoma. He has received the initial cycle of chemotherapy, consisting of rituximab, cyclophosphamide, vincristine, and prednisone, with a good response.

DISCUSSION

Once a group of diseases with an invariably early fatal outcome, PIDs have become less feared because of significant progress in diagnosis, treatment, and management. Most patients with PIDs now have the possibility of a normal life expectancy and good quality of life. This increased survival is the result of improved detection of infectious diseases, the use of antibiotics and immunoglobulins as prophylaxis against infections, the availability of potent antimicrobial agents, and definitive treatment of their diseases (eg, bone marrow transplantation). The absence of frequent infections might favor discontinuing the regular evaluation by the clinical immunologist, a mistake made clear by the example of the patient with

WAS reported here. The decision of how often a patient with a PID should be evaluated depends on several variables, including the specific disease, the presence and severity of chronic conditions, the clinical history, and the age of the patient. An expert committee of the American Academy of Asthma, Allergy & Immunology published guidelines for the management of PIDs,¹ which include the following statement:

Summary statement 29: Frequent evaluation by a clinical immunologist with applicable experience is important for patients with immunodeficiencies. Evaluations should be conducted regularly (at least every 6–12 months) by a clinical immunologist with training and experience in the care of patients with primary immunodeficiency.

Physical examination should include careful inspection for signs of infection. Despite gamma globulin replacement, respiratory tract infections may occur. Pulmonary function should be measured serially. Deteriorating function is an indication for a chest radiograph or computed tomogram (CT). Some advocate periodic chest CTs even with preserved function, because progressive abnormalities may be observed and may require intensification of treatment. Depending on the particular immunodeficiency, symptoms and signs of autoimmune disease or malignancy should also be sought. The presence of lymphadenopathy or splenomegaly may be signs of lymphoproliferative disease or malignancy.

This recommendation emphasizes the need for vigilance for 3 categories of diseases: infectious diseases, autoimmune conditions, and malignancy. Patients with PIDs are at continuous risk of autoimmune disease or malignancy. For example, in patients with WAS, autoimmune disease occurs in up to 40% of patients, and malignancy, especially lymphoma, occurs in 13% of patients.² Patients with partial DiGeorge syndrome might also have autoimmune disease.³ B-cell disorders, such as CVID, have been associated with increased risk of autoimmune disorders and malignancy.⁴ In addition, patients with CVID might present with progressive granulomatous lung disease and would benefit from early intervention and treatment.

The patient with WAS described in this article sustained a 4-year gap in specialty care. If he had continued to be regularly evaluated every 6 months by a clinical immunologist, the abnormal growth of his neck mass might have led to an earlier detection of his B-cell lymphoma and might have had the benefit of earlier therapy to stop progression of the B-cell lymphoma to tumor stage 2, thus giving him a better prognosis. We recommend evaluating patients with PIDs at least every 6 months with a complete history and physical examination, including imaging and immunologic studies appropriate for the specific immunodeficiencies. These regular evaluations would also be opportunities to provide education to the patient regarding increased risks of potential diseases associated with immunodeficiency and to reinforce the importance of compliance with maintenance

medications for the prevention of infections. Additional support for continuity of care can be obtained from lay organizations, such as the Immune Deficiency Foundation and the Jeffrey Modell Foundation, which help patients and families to understand the immune system and be aware of the late complications of PIDs.

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