

Case Report

Thymoma and cellular immune deficiency in an adolescent

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Thymoma has been associated with both humoral immunodeficiency and cellular immunodeficiency, but the latter association has never been described in the pediatric age group. We report a 15-year-old female with thymoma, recalcitrant oropharyngeal candidiasis, recurrent generalized cutaneous herpes simplex virus type 2 infection, recurrent pneumonia and myasthenia gravis. Pathology of the thymic lesion showed a 10×5×6 cm extensively hyalinized mass with residual regions of spindle cell predominant and lymphocyte-rich thymoma. There was no evidence of humoral immunodeficiency but there was clinical and laboratory evidence of cellular immunodeficiency with cutaneous anergy and absence of T cell proliferation to *Candida* antigen. Six weeks after the thymoma was resected, she was no longer anergic and *Candida* proliferation was normal, although she continued to experience infections. This is the first reported pediatric patient with an association of cellular immunodeficiency with thymoma.

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Two types of immunodeficiency have been associated with thymoma: hypogammaglobulinemia (Good's Syndrome) and cellular immunodeficiency. Good's Syndrome usually presents initially in adult patients (1, 2), although it has been described in children as young as 8 years old (3). In contrast to the occurrence of thymoma and hypogammaglobulinemia in the pediatric age group, no patient younger than age 34 years has been described with thymoma and cellular immunodeficiency (2, 4).

We report the first pediatric patient with evidence of cellular immunodeficiency in association with thymoma, a 15-year-old female with recalcitrant candidiasis and recurrent herpes simplex infections who also developed myasthenia gravis.

Case report

The patient is a 15-year-old, previously healthy African-American female with a history of chronic oral candidiasis unresponsive to clotrimazole and fluconazole for 7 months. Because of this infection, immunologic testing was performed after 3 months of recalcitrant thrush and showed an absolute CD4 count of 478 cells/mm³ and negative serology for

HIV. Over the same period, she experienced the gradual onset of proximal muscle weakness. After 7 months of persistent thrush, she presented with a 2-day history of fever and respiratory distress. Physical examination was notable for white plaque on the oral mucosa and scattered rales. She was hypoxic and was intubated. It was noted during intubation that she had thrush (later cultured as *Candida albicans*) extending deep into her pharynx. Radiographs of the chest revealed atelectasis, pneumonia, and a mediastinal mass. She developed vesicles on the perineum which spread to the legs, abdomen and arms. Herpes simplex virus type 2 (HSV-2) was identified by culture. She was treated with acyclovir, amphotericin, ciprofloxacin, cefotaxime and gentamicin and showed gradual improvement.

Thoracotomy was performed and a 10×6×5 cm, well-circumscribed mediastinal mass was resected. Histologically, the mass was largely necrotic, hyalinized and calcified, with small peripheral regions of classic lymphocyte-predominant and spindle cell thymoma (Fig. 1).

She recovered and was discharged on acyclovir and fluconazole. Two months after discharge, she developed generalized malaise and weakness pro-

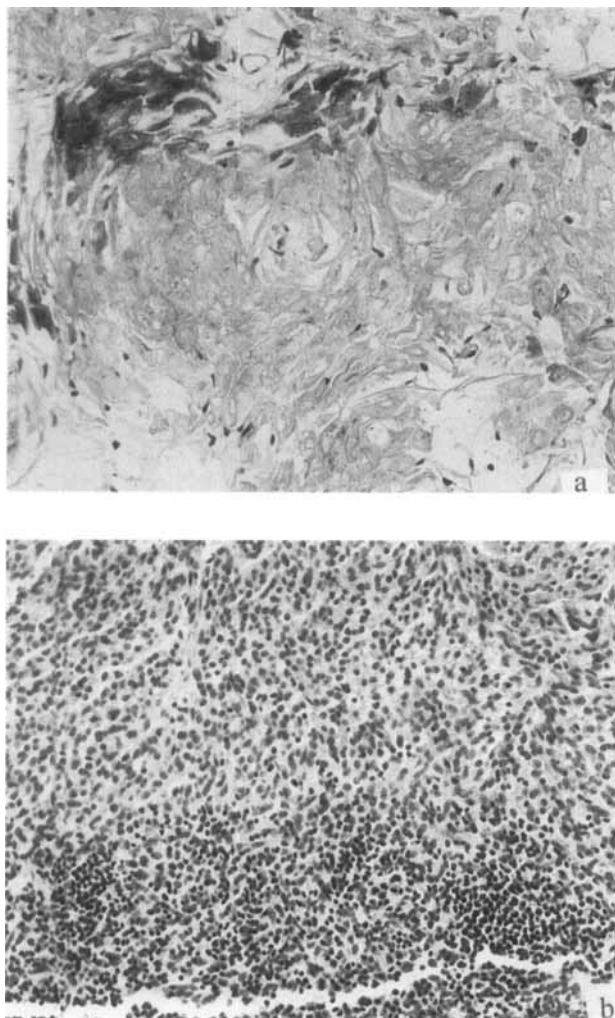


Fig. 1. The majority of the tumor was composed of necrotic nests of ghost-like epithelial cells accompanied by abundant calcification (a). Small areas within this large tumor showed histologic features classic for lymphocyte-predominant and spindle-type thymoma (b). Proliferating thymic epithelial cells accompanied by a minor lymphocytic component characterize these regions (magnification is 250 $\times$).

gressing over 1 week. Vesicles recurred on the finger, arm and foot. A positive edrophonium test confirmed myasthenia gravis. Her vital capacity was markedly low, pneumonia was diagnosed and she required intubation for respiratory support. She was treated with antibiotics, acyclovir, prednisone and pyridostigmine bromide and improved. After discharge, she required chronic therapy with prednisone and pyridostigmine bromide. She experienced two more episodes of culture-proven cutaneous HSV-2 infection and a mild episode of oro-pharyngeal candidiasis over the following 10-month period.

Review of past history failed to show any chronic or unusual infections in childhood. There was no previous history of skin, nail or vaginal yeast infections. The family history was non-contributory.

Laboratory evaluation

At the time of the first admission, the white blood cell count was 25 000 cells/mm³ with a differential of 27% band forms, 43% neutrophils, 19% lymphocytes (absolute lymphocyte count 4 750 cells/mm³), and 11% mononuclear cells. T cell enumeration performed 1 month prior to admission revealed CD4-31% (normal, 34–56%); CD8-27% (normal, 18–32%); absolute CD4-498 cells/mm³. T cell proliferation to mitogens and to *Candida* antigen was performed 1 week and 6 weeks after thymectomy, but prior to treatment with prednisone. There was a normal response to T cell mitogens: phytohemagglutinin, 23 539 cpm [normal range, (95% confidence interval) 23 679 to 114 940 cpm]; concanavalin A, 12 676 cpm (normal, 10 523 to 63 632 cpm) and Staphylococcal protein A, 32 062 (normal, 9 852 to 67 922 cpm). There was no response to *Candida* antigen at the time of initial evaluation, but 6 weeks after removal of the thymic tumor, her T cell proliferation to *Candida* antigen was normal (Fig. 2). An anergy panel (Multitest[®] CMI[™]; Connaught Laboratories, Inc., Swiftwater, PA, USA) was negative 1 week after removal of the tumor but became positive to Tetanus toxoid and *Proteus* antigen 5 weeks later. There was no response to *Candida* antigen on either occasion.

Humoral immune function was normal. Serum immunoglobulin levels were normal; IgG was 1470 mg/dl (690–1620), IgA was 362 mg/dl (70–380),

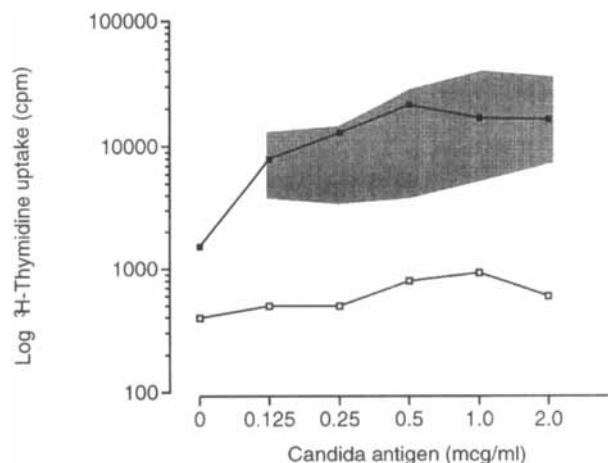


Fig. 2. T cell proliferation to *Candida* antigen at 1 (open squares) and 6 weeks (solid squares) after removal of thymic tumor. The shaded area represents the normal range (95% confidence interval).

Table 1. Antibody response to immunization

Antigen	Antibody	
	Pre-vaccination	Post-vaccination
Tetanus toxoid (IU/ml)	0.22	>3.52
Diphtheria toxoid (IU/ml)	0.16	>10.2
Pneumococcus (ng/ml)		
Serotypes		
1	743	1008
3	88	594
6	588	4659
7f	601	1391
8	187	1832
9n	442	3160
12f	917	2352
14	742	3313
18c	251	1124
19f	567	920
23f	661	6934
4	1451	3442

and IgM was 200 mg/dl (60–260). She had protective levels of antibody to *H. influenzae* type b (1.6 mcg/ml) and a positive rubella titer. Lastly, she had normal antibody responses after booster doses of tetanus and diphtheria toxoids, and a first immunization with pneumococcal vaccine (Table 1). Antibodies to skeletal muscle and acetylcholine receptors were positive in high titer.

Discussion

Thymoma, a neoplasm of thymic epithelial cell origin, usually presents in the fourth to sixth decades of life and is very uncommon in childhood. Malignancy, which is proven by evidence of invasion or metastasis, occurs in up to 35% of cases. There are multiple histopathologic variants of thymoma, but the two main types are spindle cell and lymphocyte-rich. Close to 40% of patients with thymomas experience related illnesses including myasthenia gravis, pure red cell aplasia, other autoimmune disorders and immunodeficiency.

Thymoma has been associated with both humoral and cellular immunodeficiency. Approximately 10% of patients with thymoma have hypogammaglobulinemia. The association of hypogammaglobulinemia with thymoma has been termed "Good's Syndrome", as it was first described by Good in 1954 (5). Jeunet & Good (1) reviewed the clinical manifestations of 20 such patients with this association whose ages ranged from 25 to 77 years (mean, 50 years). Clinical manifestations include sinopulmonary infections and diarrhea, myasthenia gravis, pure

red cell aplasia, thrombocytopenia and neutropenia (1, 2, 5). Laboratory evaluation of patients with Good's Syndrome typically reveals panhypogammaglobulinemia with antibody deficiency. The pathophysiology is not fully defined, but both an absence of functional B cells and an over-expression of T cell suppressor activity have been described (6–10). The histologic findings in 15 of 19 thymomas studied were that of spindle cell thymoma. Thymectomy did not relieve the hypogammaglobulinemia in any case. The youngest patient reported with Good's Syndrome was an 8-year-old boy with hypogammaglobulinemia and lymphopenia who died of disseminated varicella (3). The patient in the current report had no evidence of humoral immunodeficiency based upon normal levels of serum immunoglobulins and normal responses to immunization.

Thymoma has also been associated with cellular immunodeficiency without hypogammaglobulinemia. Clinically, thymoma and cellular immunodeficiency has been described in association with infections such as chronic mucocutaneous candidiasis, cytomegalovirus infections, herpes virus infections, and *Pneumocystis carinii* pneumonia (1, 2, 4). Associated disorders have included myasthenia gravis, aplastic anemia, and systemic lupus erythematosus (1, 2, 4). In contrast to the adolescent reported here, the previously reported patients with thymoma and cellular immunodeficiency have all been adults over 34 years of age. Although the diagnosis of thymoma sometimes precedes the clinical manifestations of immunodeficiency, most patients, like ours, come to medical attention because of the infections (1, 2, 4). Delayed-type hypersensitivity and/or *in vitro* T cell proliferative responses to *Candida* are abnormal in just over half of patients (4). Thymectomy has not resulted in resolution of cellular immunodeficiency among the previously reported patients (2, 4). In our patient, laboratory evidence of immunodeficiency (delayed-type hypersensitivity and T cell proliferation to *Candida* antigen) improved with time, although she still showed clinical evidence of cellular immunodeficiency.

The histopathologic features of this patient's thymoma were unusual in that the majority of the lesion was composed of hyalinized, necrotic and calcified epithelial cells. While malignant thymomas were reported in 55% of 27 patients with candidiasis and thymoma reviewed by Kirkpatrick & Windhorst (4), our patient had no evidence of malignancy. There has been no relationship between the specific histologic type of thymoma and the form of the immunodeficiency (2, 4).

In summary, we report the first pediatric patient with thymoma and cellular immunodeficiency. This association should be considered in the differential diagnosis of cellular immunodeficiency in children.

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