

A 15-year-old boy with severe combined immunodeficiency, fungal infection, and weight gain

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) outcomes in X-linked severe combined immune deficiency are most effective when performed with patients <3 months of age and without coexisting morbidity, and with donor cells from a matched sibling. Even under such favorable circumstances, outcomes can be suboptimal, and full cellular engraftment may not be complete, which results in poor B or natural killer cell function. Protein losing enteropathies can accompany persistent immune deficiency disorders with resultant low serum globulins (immunoglobulin A [IgA], IgG, IgM) and lymphopenia. Patients with immune disorders acquire infections that can be predicted by their immune dysfunction. Fungal infections are typically noted in neutropenic (congenital or acquired) and T-cell deficient individuals. Coexisting fungal infections are rare, even in hosts who are immunocompromised, and they require careful evaluation. Antifungal treatment may result in drug-drug interactions with significant complications.

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Chief Complaint

A 15-year-old boy with a history of severe combined immune deficiency (SCID) presented with increased weight gain, cough, and headache. He received hematopoietic stem cell transplantation (HSCT) on the 22nd day of life.

History of Present Illness

The patient had cough, headache, and weight gain over 3 weeks. He had been hospitalized for 8 weeks with disseminated histoplasmosis that involved his lungs, maxillary sinuses, and right optic disk. At presentation, therapy included itraconazole (400 mg/day) and outpatient medications for bronchiectasis, protein-losing enteropathy (PLE), and hypogammaglobulinemia. He reported facial swelling, rapid weight gain, and cough with discolored sputum. A review of systems was otherwise normal. Results of a history revealed SCID diagnosis (interleukin 2 common gamma chain receptor defect) at

birth and HSCT in infancy, with good T cell but poor B- and natural killer (NK) cell engraftment. Chimerism studies showed T cells 100% donor in origin but B cells 100% host. Despite intravenous immunoglobulin replacement, he had recurrent pulmonary infections, which resulted in bronchiectasis, and he received inhaled fluticasone-salmeterol. Intestinal biopsy documented PLE associated with leukopenia, poor growth, and hypogammaglobulinemia. At 10 years of age, he was begun on low-dose oral budesonide (highest dose, 6 mg on alternate days) and subcutaneous immunoglobulin replacement with improvement of trough immunoglobulin G (IgG) levels at >700 mg/dL (Fig. 1).

Physical Examination

Vital signs were blood pressure, 111/72 mm Hg; heart rate, 96 beats per minute; respiratory rate, 24 breaths per minute; temperature, 99.4°F. Weight was 51.8 kg (23rd percentile), with a 7-kg increase over 8 weeks. Positive physical findings included hairline flat warts and new thoracic and extremity lesions. Lung auscultation revealed bilateral basal rales without wheezing.

Laboratory Results and Clinical Course

The white blood cell count was 7500 cells/mm³, hemoglobin level was 13.9 g/dL, and the platelet count was 168,000 cells/mm³. His lymphocyte and neutrophil counts were 1100 and 5700 cells/mm³, respectively. Lymphocyte phenotyping studies showed de-

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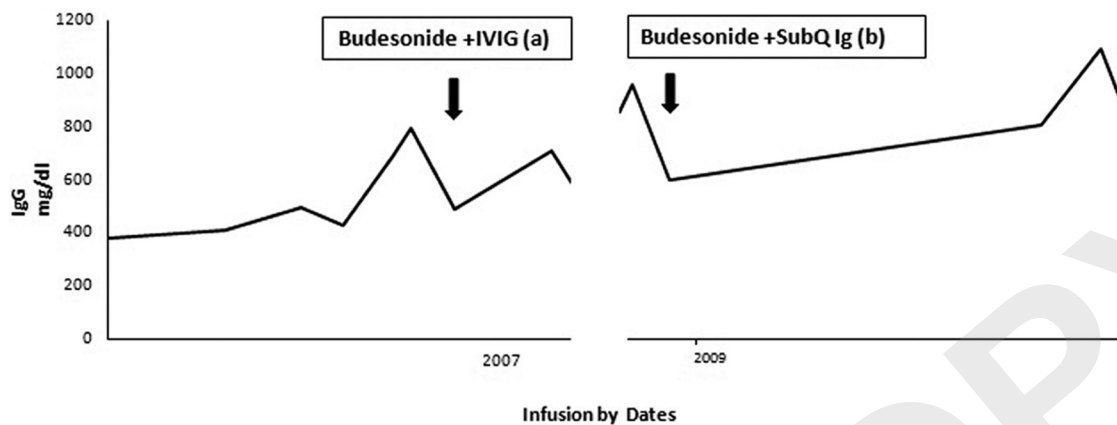


Figure 1. Trough IgG levels after PLE treatment with budesonide and intravenous immunoglobulin (a) and then budesonide and subcutaneous immunoglobulin (SubQ Ig) (b).

pressed CD4 count and absent NK cells (Table 1). There was no evidence of serum protein loss or of hepatic or renal dysfunction. The trough IgG level was 1010 mg/dL, and the serum cortisol level was consistent with adrenal suppression. Computed tomography of the chest showed new multiple tree-in-bud opacities in the bilateral lower lobes and no change in sinus disease (Fig. 2A). Sputum culture was negative for bacteria, mycobacteria, viruses, and other pathogens but positive for septated hyphae.

Question 1

What is the differential diagnosis for fungal lung disease in primary immunodeficiency disorders (PIDD)?

- (a) *Histoplasma capsulatum*
- (b) *Candida* species
- (c) *Aspergillus fumigatus*
- (d) *Cryptococcus neoformans*
- (e) Other

Differential Diagnosis

Sputum microscopy with fungal elements and elevated serum fungitell levels were consistent with *H. capsulatum* recurrence (Fig. 2 B). Examinations of urine and blood for histoplasma antigen, blood culture, and results of repeated ocular examinations were negative. Serum galactomannan and serum cryptococcal antigen results were also negative. A new pathogen, *Hormographiella aspergillata*, was isolated from sputum (Fig. 2 C).

Question 2

What further studies would one consider at this point?

- (a) Total protein, albumin level
- (b) Alanine transaminase, Aspartate aminotransferase level
- (c) Free Thyroxine, Thyroid stimulating hormone level

- (d) Brain imaging (magnetic resonance imaging)
- (e) Serum cortisol level
- (f) Serum synthetic cortisol level

The patient was below the 10th percentile for weight before admission and had received budesonide for 5 years. He developed increased weight gain after *H. capsulatum* treatment. Excess fat accumulates with weight gain when total energy intake exceeds expenditure. There was no evidence of dietary or activity change to suggest energy imbalance. Our patient, with known PIDD mutation, had no findings to indicate another genetic disorder (e.g., Prader Willi syndrome, Down syndrome). No clinical evidence of ascites, hepatic disease, or renal insufficiency was noted, and liver function and renal function studies were normal (Table 1). There was no evidence of hypothyroidism, growth hormone deficiency, hypothalamic, or pituitary lesion (data not shown: normal glucose, free Thyroxine, thyroid stimulating hormone, magnetic resonance imaging of the brain, normal height). Low serum cortisol level excluded the primary adrenal hypercortisolism as a cause of Cushing syndrome. Budesonide dosing was unchanged, but adrenocorticotrophic hormone stimulation test showed depressed adrenal response.

DISCUSSION

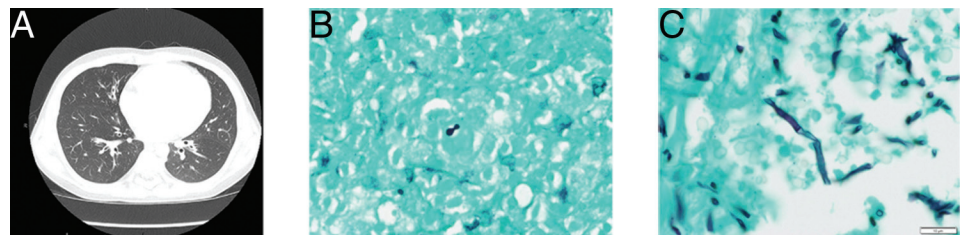
SCID-causing genetic defects disrupt numerous cellular processes, including (a) signaling pathways; (b) DNA repair mechanisms crucial for V(D)J recombination, which results in impaired T- and B-cell development; and (c) metabolic pathways that cause lymphocyte apoptosis.^{1,2} In our patient, the SCID diagnosis was made at birth with a family history of affected male family members. Despite early HSCT, neither NK nor B-cell reconstitution was achieved. He demonstrated good T-cell reconstitution but later developed

Table 1 Clinical laboratory results

Laboratory Study	Results	Reference Range
WBC	$7.5 \times 10^3/\text{UL}$	$4.5\text{--}13.5 \times 10^3/\text{UL}$
Hgb	13.9 g/dL	12.6–17.7 g/dL
Hct	43.6%	37.5–51.0%
Platelet	$168 \times 10^3/\text{UL}$	$150\text{--}450 \times 10^3/\text{UL}$
Neutrophils (ANC)	$5.7 \times 10^3/\text{UL}$	$1.4\text{--}7.0 \times 10^3/\text{UL}$
Lymphocytes (ALC)	$1.1 \times 10^3/\text{UL}$	$0.7\text{--}3.1 \times 10^3/\text{UL}$
Eosinophils (AEC)	0 cells/mm ³	$0.0\text{--}0.4 \times 10^3/\text{UL}$
CD 3 ⁺	611 cells/mm ³	1014–2557 cells/mm ³
CD 4 ⁺	208 cells/mm ³	538–1569 cells/mm ³
CD 8 ⁺	410 cells/mm ³	371–936 cells/mm ³
CD 3 ⁺ - CD 16 ⁺ /56 ⁺	0 cells/mm ³	152–595 cells/mm ³
CD 20 ⁺	162 cells/mm ³	59–457 cells/mm ³
CD 19 ⁺	155 cells/mm ³	204–703 cells/mm ³
Total protein	6.7 g/dL	6–8 g/dL
Albumin	4.2 g/dL	3.5–5.5 g/dL
BUN	18 mg/dL	5–18 mg/dL
Creatinine	0.56 mg/dL	0.12–1.06 mg/dL
ALT	63 IU/L	0–30 IU/L
AST	57 IU/L	0–40 IU/L
IgG	1010 mg/dL	641–1353 mg/dL
Serum cortisol level	0.1 µg/dL	2.3–19.4 µg/dL
Sputum culture for bacteria	Negative	
Sputum culture for mycobacteria	Negative	
Sputum viral PCR (EBV, CMV, adenovirus, RSV)	Negative	
Sputum culture for fungus	Septate hyphae (+)	
Aspergillus galactomannan	Negative	
Serum cryptococcal antigen	Negative	
Urine histoplasma antigen	Negative	
Fungitell	>500 pg/mL	<60 pg/mL
CRP	3.7 mg/L	0.0–4.9 mg/L

AEC = absolute eosinophil count; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein-Barr virus; Hct = hematocrit; Hgb = hemoglobin; PCR = polymerase chain reaction; RSV = human respiratory syncytial virus.

Figure 2. Computed tomography of the chest. (A) “Tree-in-bud” findings with fungal infection and photomicrographs of *H. capsulatum* (with Silver methenamine stains [$\times 60$]) (B), and septated hyphae as could be seen in *H. aspergillata* (with GMS [Gomori methenamine silver] stain [$\times 1000$]) (C).



PLE, which resulted in reduced serum concentrations of albumin, serum globulins (IgA, IgG, IgM), lymphopenia, and chronic sinopulmonary disease.

At 8 years of age, he developed human papilloma-virus-associated flat warts on his face and trunk. Host defense against HPV relies on intact and functioning

cellular immunity, including T- and NK-cell cytotoxicity. Our patient did not have other infections, such as Epstein-Barr virus, Herpes simplex virus, or cytomegalovirus, associated with his NK-cell deficiency.^{3,4} Infection susceptibility in PID is often predicted by the nature of the immune defect.⁵ Pulmonary infections

Table 2 Drug interactions with steroids

Drugs	Mechanism of Action	Adverse Effect
Amphotericin B	Steroids increase the hypokalemic effect of amphotericin B	Hypokalemia
CYP3A4 inhibitors Azoles: itraconazole, ketoconazole, posaconazole, voriconazole; clarithromycin, ritonavir, telaprevir, chloramphenicol	Inhibition of steroid metabolism	Increased steroid effect, Cushing syndrome
CYP3A4 inducers Carbamazepine, fosphenytoin, nevirapine, rifampin)	Increase in steroid metabolism	Decreased steroid effect

CYP3A4 = Cytochrome P450 3A4.

Glucocorticoids undergo metabolism in the liver and other tissues by CYP3A4 and other transformations; medications that strongly inhibit or induce CYP3A4 may significantly alter the glucocorticoid serum concentration.

with pyogenic bacteria occur frequently in antibody deficiency disorders. After switching to subcutaneous immunoglobulin replacement, serum immunoglobulin levels stabilized but the frequency of sinus infections persisted, likely due to his absent serum IgA. Fungal infections are more commonly seen in T-cell and neutrophil defects. Our patient's risks for fungal infection included hypogammaglobulinemia and lymphopenia but not neutropenia.

Invasive aspergillosis is the most common cause of mortality due to major invasive mycoses. *A. fumigatus* is the most frequently isolated pathogen in pulmonary disease with reports in chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion deficiencies, idiopathic CD4 lymphocytopenia, and Good syndrome.⁵⁻⁷ Histopathology demonstrated narrow septated hyphae with dichotomous acute angle branching. A definitive diagnosis requires organism isolation (blood or tissue). A positive serum galactomannan can predict invasive disease with 90% sensitivity and 98% specificity.

Candida species are another important cause of fungal infection in patients who are immunocompromised. *Candida* species predominantly presents with yeast morphology. Most species produce pseudohyphae but *Candida albicans* and *Candida dubliniensis* can produce true hyphae. The most-frequent invasive presentation is fungemia but pulmonary and cardiac infections are reported after hematogenous dissemination or showering of septic thrombi. *Candida* infections are reported in hyper-IgE syndrome, SCID, major histocompatibility complex II deficiency, X-linked ectodermal dysplasia, myeloperoxidase deficiency, and severe congenital neutropenia.^{5,6}

Cryptococcus neoformans is a round, encapsulated basidiomycete. The most common clinical presentation of cryptococcal infection is meningoencephalitis, followed in incidence by pulmonary infection. Sputum

culture has low sensitivity, and definitive diagnosis requires tissue examination and culture. Serum cryptococcal antigen is typically nondetectable in isolated organ disease. Cryptococcal infections are reported in idiopathic CD4 lymphocytopenia, hyper-IgE syndrome, and Good syndrome with associated white cell aplasia.⁵⁻⁸

In our patient, sputum culture revealed septated hyphae and a new pathogen *H. aspergillata* was isolated. The genus *Hormographiella*, first described by Guarro *et al.*,⁹ is a member of the basidiomycete genus. Microscopically septated hyaline conidiophores bearing conidiogenous hyphae may be observed.¹⁰ This fungus grows at 37°C, mostly occurring in compost and sewage. It is an uncommon human pathogen (13 reported cases), mostly found in patients with hematologic malignancies and after HSCT, with or without neutropenia.^{11,12} Lungs are the primary infection site, followed by skin, eye, and brain. Coinfections of *H. aspergillata* with *Rhizomucor variabilis*¹³ and *Aspergillus flavus*¹⁴ are reported. However, coinfection of *H. capsulatum* and *H. aspergillata* has not been reported. The history of environmental exposure to wet, malodorous, blackened flooring during home remodelling explains exposure risk for this youngster's isolated pathogens.

Weight gain with fungal disease is uncommon. Endocrine causes of obesity and/or weight gain are infrequently identified in children and include growth hormone deficiency, hypothyroidism, pseudohypoparathyroidism, cortisol excess, and acquired hypothalamic lesions. Very low serum cortisol level (Table 1) eliminated adrenal hyperfunction as a cause of weight gain in this patient.

The most common cause of iatrogenic CS in nonendocrine diseases is prescribed oral steroids but injected, topical, and inhaled glucocorticoids have also been associated. Glucocorticoid clearance can be af-

fects by medications (Table 2), with varying clinical effects, and iatrogenic adrenal insufficiency related to azole and budesonide is reported.¹⁵ Azoles are strong inhibitors of cytochrome-P450–dependent CYP3A4, which is involved in budesonide metabolism. In our patient, it is likely that budesonide metabolism was reduced secondary to combined budesonide-itraconazole therapy, which caused iatrogenic CS. Analysis of the data indicates that increased synthetic glucocorticoid levels resulted in further immune suppression and *H. aspergillata* growth and weight gain. Adrenocorticotrophic hormone stimulation testing was performed to evaluate adrenal function and supported the diagnosis of iatrogenic CS. Oral budesonide was weaned, with absent synthetic glucocorticoid levels documented. Continued oral azole and inhaled amphotericin B improved his fungal infection. He required a marked increase in subcutaneous immunoglobulin dosing for worsening PLE.

Final Diagnosis

The final diagnosis was azole-budesonide–induced iatrogenic CS with *H. aspergillata* pulmonary infection.

CONCLUSION

Numerous medications have been shown to impact steroid metabolism (Table 2). In PID, azole therapy is commonly used as prophylaxis or acute treatment of fungal infections. Initiation of azole therapy in patients who are immune deficient should prompt review of all forms of steroid use. Drug-drug interactions that alter glucocorticoid metabolism can cause iatrogenic CS and significant morbidity. In our patient with interleukin 2 common gamma chain receptor defect SCID and lymphopenia, interactions of azoles with glucocorticoids (oral, topical, inhaled) affected the disease course and response to treatment. Our patient, to date, has survived an almost universally fatal fungal pathogen, *H. aspergillata*.

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