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Traveler's Pneumonia Case Study

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An 11-year-old girl from Michigan took a 3-week summer vacation to the southwest United States (figure 1, map), and upon returning, developed a progressively worsening productive cough and weight loss. She was admitted to the hospital 3 weeks after becoming symptomatic. Her brother had a similar illness [6].

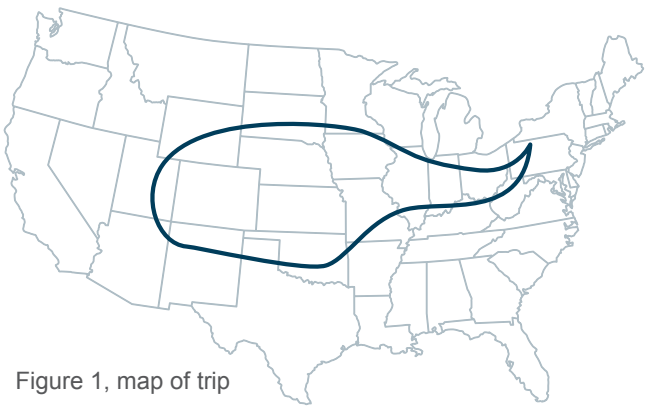

Figure 1, map of trip

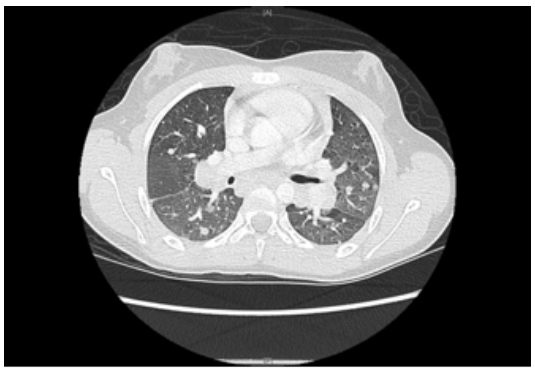

Figure 2

Chest radiographs in the patient showed diffuse linear opacities at the base of the lungs (figure 2). Bronchoalveolar lavage fluid fungal and mycobacterial cultures were negative. She was treated empirically with fluconazole for presumed coccidioidomycosis based on travel history. However, anti-*Coccidioides* antibodies measured by complement fixation, immunodiffusion and MVista® antibody enzyme immunoassay (EIA) [7, 8] results were negative initially and upon repeat testing one week later. *Coccidioides* serum antigen was negative.

Blastomyces serum antigen was positive (0.8 ng/mL) initially and became negative 6 weeks later. *Blastomyces* IgG antibodies measured by MVista® *Blastomyces* Antibody EIA were negative initially and 6 weeks later.

Histoplasma serum antigen was positive (1.3ng/mL) initially and negative a week later while urine antigen was negative initially and one week later. Anti-*Histoplasma* complement fixation antibody was positive at a titer of 1:16 at one month. Anti-*Histoplasma* immunodiffusion antibody was negative initially and positive at 6 weeks. Anti-*Histoplasma* IgM antibodies

measured by the MVista® IgM were undetectable. Anti-*Histoplasma* IgG antibody was positive on admission (23.0 EIA units), 42.1 EIA units at 1 week, and increased to >80.0 EIA units at 6 weeks. These findings support the diagnosis of acute pulmonary histoplasmosis.

Additional history obtained after the diagnosis was established revealed that she and her brother had ridden 3-wheelers on dirt roads in Michigan a few weeks before traveling to the Southwestern United States.

The patient was treated with liquid itraconazole (400mg daily), and prednisone (50mg daily) was added 2 weeks later for persistent cough despite negative *Histoplasma* antigen results, improvement in pulmonary lesions, and itraconazole compliance. Itraconazole blood levels were measured and were in the therapeutic range. Itraconazole was continued for an additional 3 months after prednisone was discontinued.

Histoplasmosis Diagnostic Approach.

Dozens of studies have been conducted to evaluate clinical manifestations, laboratory findings and treatment for histoplasmosis in adults. Historically, the data on pediatric histoplasmosis had been limited to case studies in retrospective reporting of 8 cases described at 1 academic medical center [9]. *Histoplasma* antigen was detected in the urine of all 4 disseminated cases but not in pulmonary cases.

More contemporary data has been published from investigators at Nationwide Children's Hospital and Ohio State University from a retrospective analysis of 73 children, including 17 proven and 56 probable cases [10]. Diagnostic studies are summarized in table 1. Diagnostic testing results in children are compared with those in adults based on clinical manifestations in table 2. The adult study was a retrospective analysis of 218 patients for whom *Histoplasma* antigen testing was performed at MiraVista Diagnostics as part of the diagnostic evaluation [4].

Table 1. Results of diagnostic tests in the Nationwide pediatric study

Test	Immunocompetent	Immunocompromised
Urine antigen	7/40 (18%)	8/13 (62%)
• Pulmonary	5/31 (16%)	2/5 (40%)
• Disseminated	2/9 (22%)	6/8 (75%)
Serum antigen	11/35 (31%)	9/13 (69%)
• *Pulmonary*	9/25 (36%)	2/4 (50%)
• Disseminated	2/10 (20%)	7/9 (78%)
Complement fixation	47/53 (87%)	12/15 (80%)
• Pulmonary	38/41 (93%)	5/7 (71%)
• Disseminated	9/12 (75%)	7/8 (88%)
Immunodiffusion	40/53 (75%)	8/15 (53%)
• *Pulmonary*	32/41 (78%)	2/7 (29%)
• *Disseminated*	8/12 (75%)	6/8 (75%)
Histopathology (lymph nodes, lung)	10/17 (59%)	5/7 (71%)

When comparing results from the pediatric and adult studies, antigen detection was less sensitive in the pediatric population (Table 2). Twenty-two percent of children were immunocompromised in the pediatric study and the causes for immunocompromise included chemotherapy for malignancy in 5 patients and rheumatologic or gastrointestinal disorders requiring treatment with tumor necrosis factor alpha or corticosteroids in 11 patients [10]. In contrast, seventy-two percent of adults were immunocompromised [4] including underlying AIDS in 36%, solid organ transplantation in 17%, hematologic malignancy in 9%, other immunodeficiencies in 7% and tumor necrosis factor treatment in 15% or treatment of other medical conditions with immunosuppressive medications, mostly corticosteroids in 17%. Thirty-seven percent of "immunocompetent" adults had chronic diseases or were elderly [4], both which may reduce immune response. Antigen was detected in the urine of 94% of adults and 62% of children who were immunocompromised and 73% of adults and 18% of children who were immunocompetent.

Table 2. Comparison of diagnostic tests in children [10] and adults [4].

Test	Pulmonary children	Pulmonary adult	Disseminated children	Disseminated adult
Antigen-urine	7/36 (19%)	26/60 (43%)	8/17 (47%)	145/158 (92%)
Antigen-serum	11/29 (38%)	None	9/19 (47%)	31/31 (100%)
Immunodiffusion	34/48 (71%)	31/49 (63%)	14/20 (70%)	21/61 (34%)
Complement fixation	43/48 (90%)	40/50 (80%)	16/20 (80%)	52/73 (71%)

Pediatric Study Key Points:

Culture: blood cultures yielded no growth of H. *capsulatum* (0/63). BAL (1/13) and sputum cultures (1/5) were of low yield. Recommend additional diagnostic testing.

Serology: CF or ID yielded probable diagnosis in 93% of patients tested, having a CF titer ≥1:32 in 74%. Recommend: serology is useful in diagnosis of histoplasmosis in pediatric population.

Antigen: reported antigenemia (38%) and antigenuria (19%) in children were lower than published results in adults (69%) [1], however, this adult study comprised adults with heavy exposure, reducing comparability of sensitivity with the two study populations. Severe disease occurred in 21% of the patients, and the majority were immunocompetent. Published studies have found antigen detection varies depending on immune status and severity of disease [2-4].

Overall Recommendation: Diagnosis should neither be made nor excluded based on the results of one diagnostic test.

- Testing serum and urine antigen, serology and culture increase diagnostic yield for histoplasmosis[5]
- Invasive procedures to obtain tissue for histopathology can be reserved if other diagnostic methods yield inconclusive results for determination of diagnosis.

IMMUNOCOMPROMISED VS IMMUNOCOMPETENT:

- Immunocompromised (IC) children: more disseminated histoplasmosis, more prolonged hospitalizations, higher antigen concentrations in serum and urine and prolonged antigen detection compared with immunocompetent patients. These findings are similar to other published reports [4].

Summary:

The cases emphasize the importance of a careful history eliciting the onset of symptoms and travel history. Data from both studies emphasize the importance of utilizing more than one test to diagnose histoplasmosis in both children and adults. From previous studies[4, 11] testing both antigen and antibody achieve highest sensitivity for diagnosis in adults. Limitations of these studies include retrospective design, different diagnostic approaches and antibody testing in multiple laboratories. More studies are needed in children to ascertain the performance characteristics of the antigen assays in different manifestations of histoplasmosis.

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