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CASE REPORT

Variable urine *Histoplasma* antigen with volume status

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ABSTRACT

A patient with progressive disseminated histoplasmosis was noted to have an increase in urine *Histoplasma* antigen level during monitoring of her disease. The patient revealed she had inadequately hydrated, and her urine volume was low and subjectively concentrated. Following hydration, urine antigen was retested and became undetectable.

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1. Case report

A 42-year-old woman with ulcerative colitis on high-dose infliximab was diagnosed with progressive disseminated histoplasmosis at two weeks postpartum. Her unusual case involved vertical transmission of histoplasmosis to her child and has been previously reported [1]. Given fever and systemic symptoms with nodular infiltrate on chest imaging and laboratory evidence of anemia and hepatitis, she was treated with intravenous Amphotericin B for two weeks and then transitioned to itraconazole capsules. Initial urine histoplasma antigen (UHAg) was >19 ng/ml, which is above the limit of quantification (LoQ) for the MiraVista assay used (scale of results: Negative; Positive – below the LoQ <0.4 ng/ml; Positive – 0.4–19 ng/ml; Positive – above the LoQ >19 ng/ml; *Histoplasma* Quantitative Enzyme Immunoassay). Her itraconazole levels were monitored every 3–4 months and were in therapeutic range throughout her treatment, and she clinically improved [Figure 1].

At her 12-month follow-up visit, UHAg was measured at 1.81 ng/ml. Itraconazole was continued due to her significant immunosuppression at diagnosis, high antigen levels at diagnosis, and persistently positive UHAg. UHAg subsequently increased at month fifteen to 3.07 ng/ml. During the discussion of results, the patient noted that she was subjectively volume depleted, resulting in a low-volume, concentrated-appearing urine specimen. She increased water intake and provided a repeat sample seven days later that showed a 'Negative' UHAg result [Figure 1].

Histoplasmosis is a common fungal infection in the Ohio and Mississippi River Valley regions caused by inhalation of *Histoplasma capsulatum* with a wide range of clinical manifestations [2]. Immunosuppressed patients are at higher risk for the development of progressive disseminated histoplasmosis [2]. While culture remains the gold standard for diagnosis, its sensitivity is limited. Thus, antigen detection assays utilizing serum, urine, bronchoalveolar lavage, and cerebrospinal fluid have emerged as an effective tool for the diagnosis of active infection [3].

While UHAg testing has a high sensitivity of 91–95%, unexpected variability of UHAg during monitoring of disease has been reported [4,5,6]. Fluctuating urine concentrations have been hypothesized as a cause of this variability; however, no study has directly evaluated the physiologic concentration of urine and effects on antigenuria [5,6]. One study, conducted to evaluate if ultrafiltration of false-negative UHAg samples improved detection rates, concluded that ultrafiltration increases antigen detection in previously false-negative samples [7]. This research supports the theory that dilution of urine may result in reduced sensitivity of antigen detection. Given the effects of urinary concentration on antigen detection, we hypothesize that the variability of this patient's UHAg may be related to her volume status and urine concentration. Alternatively, it is possible that this variability may have been a laboratory error.

If levels of urine antigen do vary based on concentration as has been suggested in this case report and in the ultrafiltration study, volume status should be considered when interpreting UHAg testing, which can be of considerable importance in both inpatient and outpatient populations [7]. Urine dilution may lead to more false-negative results than previously appreciated, and conversely, increased urinary concentration may lead to spuriously elevated results, complicating interpretation of treatment response. Determining whether urine dilution

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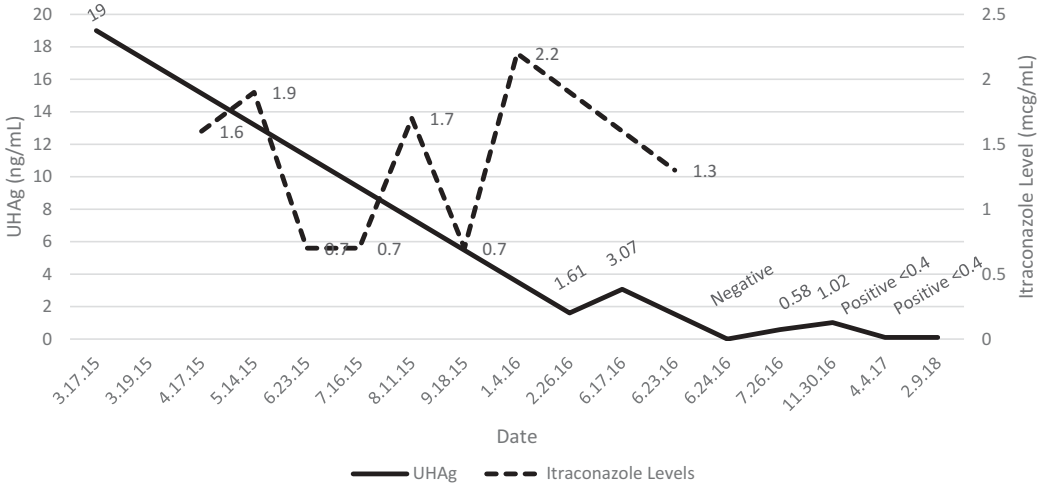

Figure 1. UHAg and itraconazole levels over time.

affects antigenuria to a clinically significant degree is especially important since many patients with progressive disseminated histoplasmosis are volume resuscitated when initial testing occurs. Further study is warranted to determine if urine concentration affects urine antigen levels and its subsequent clinical significance.

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