Red-Brown Urine in a Patient with Chronic HIV Infection and Quadriparesis

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CASE DESCRIPTION

A 42-year-old woman with chronic HIV infection presented with sudden onset of progressive limb weakness, leading to immobility within 4 days. This was preceded by severe abdominal pain, nausea, and vomiting for 2 days and episodes of confusion and agitation.

Six weeks prior, she had commenced highly active antiretroviral therapy (HAART),4 consisting of efavirenz/emtricitabine/tenofovir and cotrimoxazole for opportunistic infection prophylaxis. Additional history included constipation for 4 weeks and an admission for psychiatric symptoms 1 week before starting HAART. She had declined HAART when HIV infection was diagnosed 6 years earlier, but was successfully treated for multidrug-resistant tuberculosis.

Examination revealed bilateral facial-nerve palsies, quadriparesis, global areflexia, absence of proprioception, and patchy loss of sensation below T4. MRI excluded focal lesions and progressive multifocal leukoencephalopathy. The patient was apyrexial and normotensive with a tachycardia of 133 beats per minute and diaphoresis. Cerebrospinal fluid (CSF) showed increased total protein of 1.25 g/L (reference interval 0.15– 0.45 g/L) without white blood cells and no evidence of opportunistic infection (Table 1). Complete blood count, and renal and liver function tests were unremarkable except for hypoalbuminemia of 28 g/L (reference interval 35–52 g/L). Vitamin B12 was within the reference interval and serum iron studies suggested anemia of chronic disease. Serology was negative for hepatitis A and C, indicating only past hepatitis B infection. Tests for cytomegalovirus and syphilis were negative.

Since commencing HAART, the CD4 count had risen from 79 to 109 × 10^6/L and the HIV viral load had declined from 105 224 to 235 copies/mL (decrease of 2.65 log). This prompted consideration of the Guillain-Barré syndrome (GBS) variant of neurological immune reconstitution inflammatory syndrome (IRIS). In spite of a 5-day course of intravenous immunoglobulin, the clinical condition deteriorated, culminating in respiratory distress necessitating mechanical ventilation. Antiganglioside antibodies were negative and examination of the stool excluded infection with Campylobacter and other pathogens (Table 1). During the patient’s stay in the ward, her urine was noted to have a red-brown color not explained by myoglobinuria because creatine kinase was only slightly increased at 229 U/L (reference interval 20 –180 U/L). However, microscopy of catheter urine samples demonstrated high numbers of leukocytes, erythrocytes, and bacteria, consistent with urinary tract infection.

DISCUSSION

Benign causes of red-brown urine include intake of foods (beetroot, blackberries) and medication (rifampicin, phenolphthalein, and phenothiazines). Pathological causes are hematuria, hemoglobinuria, myoglobinuria, and porphyrinuria. Erythrocytes impart a red color to urine, which turns brown within hours due to oxidation of hemoglobin to methemoglobin, particularly at acidic pH. Because erythrocytes, hemoglobin, and myoglobin all produce a positive result in the reagent strip test for blood, hematuria must be confirmed by microscopic vi-
due to recovery of the immune system after initiating IRIS is the paradoxical worsening of a patient’s condition following a therapeutic response. A 33-year-old woman presented with quadriparesis, severe pain, nausea, and vomiting several weeks after commencing HAART. It is characterized by a robust inflammatory immune response usually directed against opportunistic pathogens, rarely autoimmune (1). GBS has been described during all stages of HIV infection, most often during the chronic phase as a manifestation of IRIS, and infrequently in the acute phase during seroconversion (1). The following features supported a diagnosis of GBS IRIS: (a) acute axonal motor neuropathy developing 6 weeks after commencing HAART, (b) 2.65 log reduction in plasma HIV viral load, (c) initial CD4 cell count <200 mm³, and (d) absence of opportunistic infection (1). Although antiganglioside antibodies were negative, they are not consistently positive in GBS IRIS and may represent an epiphenomenon during IRIS (1). Subsequent confirmation of acute porphyria ruled out IRIS. Acellular CSF with raised total protein as seen in GBS has also been described in AIP, probably the consequence of axonal degeneration and demyelination (2).

PORPHYRIA

The porphyrias arise from partial deficiencies in enzymes of the heme biosynthetic pathway. The rate-limiting step is 5-aminolevulinate synthase, which is regulated through negative feedback by heme. The acute porphyrias are characterized by neurovisceral crises triggered by drugs, alcohol, fasting, stress, and hormonal fluctuations. These factors induce 5-aminolevulinate synthase, or act indirectly by heme depletion owing to diversion toward cytochrome P450 (CYP) drug metabolism. Neurotoxicity has been ascribed predominantly to axonal damage by free radicals generated from 5-aminolevulinic acid (ALA) (3). Neurovisceral crises present with autonomic dysfunction (manifesting as abdominal pain, nausea/emesis, hypertension, tachycardia, and constipation), peripheral neuropathy, encephalopathy, and psychiatric disorders (3). Although our patient experienced abdominal pain with nausea and vomiting, these symptoms had dissipated by the time she presented with quadriparesis. This phenomenon has been described by Meissner and co-workers (4), who caution that in some patients the disappearance of pain is a harbinger of paralysis and not indicative of improvement.

Two of the acute porphyrias arise from enzyme deficiencies early in the pathway: ALA dehydratase (ALAD) in the very rare ALAD deficiency porphyria and PBG deaminase (PBGD) in AIP. In these disorders, the precursors ALA and PBG mainly accumulate, hence skin lesions are not observed. The other 2 acute porphyrias arise from deficiencies later in the pathway: coproporphyrinogen oxidase in hereditary coproporphyria (HCP) and protoporphyrinogen oxidase in variegate porphyria (VP). The unexpected increases in ALA and PBG observed in these porphyrias are caused by inhibition of PBGD activity by the metabolites, coproporphyrinogen III and protoporphyrinogen IX, just upstream of the re-
spective enzymes (5). Skin lesions, caused by photoactivation of accumulated cutaneous porphyrins, may be found. During acute attacks, urine PBG concentrations are typically >10 times the upper reference limit (3). In our patient, urine PBG >40 times the upper reference limit confirmed a diagnosis of acute porphyria. The traditional view is that normal to marginally increased fecal porphyrin excretion distinguishes AIP, because manyfold increases are expected in HCP and VP (3). However, several studies reporting significant fecal porphyrin increases in AIP have challenged this view (6). One such report proposes plasma scanning as the second-line investigation in patients with raised urinary PBG (6). Finding a peak at 623 nm confirms VP, whereas a peak at 619 nm requires determination of the fecal coproporphyrin III/I isomer ratio (FCR) to distinguish between AIP (FCR <1.55) and HCP (FCR >1.55) (6). Our patient had a plasma peak at 619 nm, but FCR measurement was unavailable. The diagnosis of AIP was confirmed by demonstrating a known mutation in the hydroxymethylbilane synthase (HMBS) gene (previously PBGD) (c.181delG; p.Asp61Thr fs*37), whereby a deletion in exon 5 creates a frameshift resulting in a premature stop codon (accession number HD040038 at www.hgmd.cf.ac.uk). We were unfortunately unable to obtain heme arginate and managed the patient conservatively. She received intensive physiotherapy once she had been weaned off the ventilator but was still bedridden 2 months later. Further investigations should be conducted on family members to identify individuals at risk of potentially fatal attacks.

The association between PCT and HIV infection in the presence of risk factors such as chronic viral hepatitis, iron overload, liver disease, and alcohol abuse is well-documented (7, 8). Biochemistry is typical of PCT: raised urine porphyrins (predominantly uro- and heptacarboxylic porphyrins) with normal PBG and increased stool porphyrins showing a series of decarboxylated intermediates and the characteristic isocoprotoporphyrin (8). As with AIP and HCP, a plasma emission peak at 619 nm may be demonstrated. Symptomatic patients may have skin lesions, but acute neurovisceral attacks do not occur. The following features were against PCT in our patient: acute neurovisceral presentation without skin lesions, no risk factors or liver pathology, increased urine PBG, and no fecal isocoprotoporphyrin band.

A literature search from 1955 revealed that this is only the fourth report of acute porphyria in HIV infection (7, 9, 10). The other 3 reports are of acute attacks of VP, triggered by nucleoside reverse transcriptase inhibitors. This is the first report of acute AIP most likely precipitated by sulfamethoxazole and efavirenz. Although sulfamethoxazole has long been known to be porphyrinogenic, reports on the effects of HAART in porphyria have just recently emerged. Among the antiretroviral drugs, those with the strongest heme-depleting effects, particularly inducers of CYP 3A4 and 2C9, are the most porphyrinogenic. These include efavirenz, nevirapine, ritonavir, and indinavir (9). Antiretrovirals that are least likely to be porphyrinogenic are tenofovir, lamivudine, abacavir, didanosine, and raltegravir (9, 10).

CONCLUSION

This case illustrates the diagnostic dilemma faced by clinicians when patients develop neuropathology after commencing HAART. Although neurological IRIS is a reasonable consideration in cases with brisk immune reconstitution, definitive diagnosis requires exclusion of drug toxicity. Because most standard HIV protocols include porphyrinogenic antiretrovirals and sulfamethoxazole, ruling out acute porphyrinic neuropathy is mandatory. For many years, PCT was the only porphyria reported in HIV infection. Our case and others similar to it highlight the importance of acute porphyrias in this setting and the need to develop antiretroviral regimens that are not only effective, but also safe, in porphyria. In addition to the use of heme arginate, nonporphyrinogenic regimens may well be important (10).

ADDITIONAL RESOURCES

Drug safety and expert clinical advice from specialist networks:

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<th>POINTS TO REMEMBER</th>
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<tr>
<td>• Red-brown urine may be caused by intake of certain foods and medications and by hematuria, hemoglobinuria, myoglobinuria, and porphyrinuria.</td>
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<td>• IRIS should be considered when rapid recovery of the immune system after initiation of HAART is associated with clinical deterioration that cannot be ascribed to a newly acquired disease or drug toxicity.</td>
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<td>• Since both neurological IRIS and porphyrnic neuropathy can present with a Guillain-Barré–like syndrome, acute porphyria should always be considered in the differential diagnosis of rapidly evolving neuropathy.</td>
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<td>• Several antiretrovirals and cotrimoxazole (sulfamethoxazole component) that are frequently prescribed in HIV infection can elicit acute porphyrnic attacks.</td>
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<td>• Plasma emission spectroscopy distinguishes between VP (peak at 623 nm) and AIP/HCP (both show peaks at 619 nm). Fecal coproporphyrin III/I ratio distinguishes between HCP (&gt;1.55) and AIP (&lt;1.55).</td>
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This case study considers the diagnostic dilemma of an acute neurological deterioration in a patient with chronic HIV infection, following the commencement of HAART. Although acute porphyria is part of the differential diagnosis, it was not considered until relatively late, which is often the case in other scenarios and reflects the rarity of acute porphyria and the relative lack of familiarity of many clinicians with these disorders.

The seminal observation was that of red-brown discoloration of the urine, which ultimately prompted measurement of urine PBG. One of the key messages is that urine PBG is the single-most-important analyte to measure, firstly as a rule-out. If urine PBG is negative, then any concomitant symptoms are not due to acute porphyria. Conversely, a positive urine PBG is specific for porphyria and should prompt further investigation. Another key message is that when porphyria is genuinely suspected, a complete set of samples is required—blood, urine, and feces because the various facets of investigation are complementary and enable a definitive diagnosis to be made.

Measurement of red-cell PBG deaminase activity (not mentioned in this case) is another approach to investigation of suspected AIP, although with significant overlap between affected and unaffected individuals. Genotyping and identification of a known PBG deaminase mutation in this case enabled a definitive diagnosis and the possibility of cascade family screening.

Although, in retrospect, most of the clinical features were consistent with AIP (abdominal pain, psychiatric symptoms, tachycardia, neurological deterioration), it is often difficult to make a unified clinical diagnosis. The case also illustrates the gravity of the condition and the need to identify possible precipitating drugs—likely sulfamethoxazole and efavirenz in this case.