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CASE REPORT

Acute Hepatic Porphyria and Systemic Lupus Erythematosus: coincidence or clinical connection?

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Introduction

Porphyrias are a group of disorders caused by deficiencies of the enzymes involved in the production of heme.[1] They are each caused by a specific abnormality in the heme biosynthesis process.[2] They can result in neurovisceral manifestations (e.g. abdominal pain, motor, and sensory peripheral neuropathy, neuropsychiatric manifestations) and/or cutaneous photosensitivity (either chronic and blistering or acute and mostly non-blistering).[3] The diagnosis of porphyrias can be challenging because they are rare and their symptoms sometimes non-specific.[3] Porphyrias can be classified into hepatic or erythropoietic, depending on whether pathway intermediates first accumulate in the liver or the bone marrow, respectively.[3] The hepatic porphyrias can present as acute hepatic porphyrias (AHP) and include Acute intermittent porphyria (AIP), Aminolevulinic acid dehydratase porphyria (ALAD), Hereditary coproporphyria (HCP) and Variegate porphyria (VP).[3,4]

In contrast, systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a variable clinical course.[5] Co-existence of an AHP and SLE is rare but has been described. As of June 2023, only 16 cases had been described and documented in literature.[6] No case in South Africa has previously been documented. The overlap of symptoms makes diagnosis difficult and a delay in diagnosis and treatment may result in significant morbidity and/or mortality. The question is whether co-existence is mere coincidence or if there is a causal bi-directional unmasking relationship? Simply put, does SLE pre-dispose to an acute porphyria flare presentation or does an acute porphyria flare evoke an SLE presentation? If so, what would putatively explain the relationship?

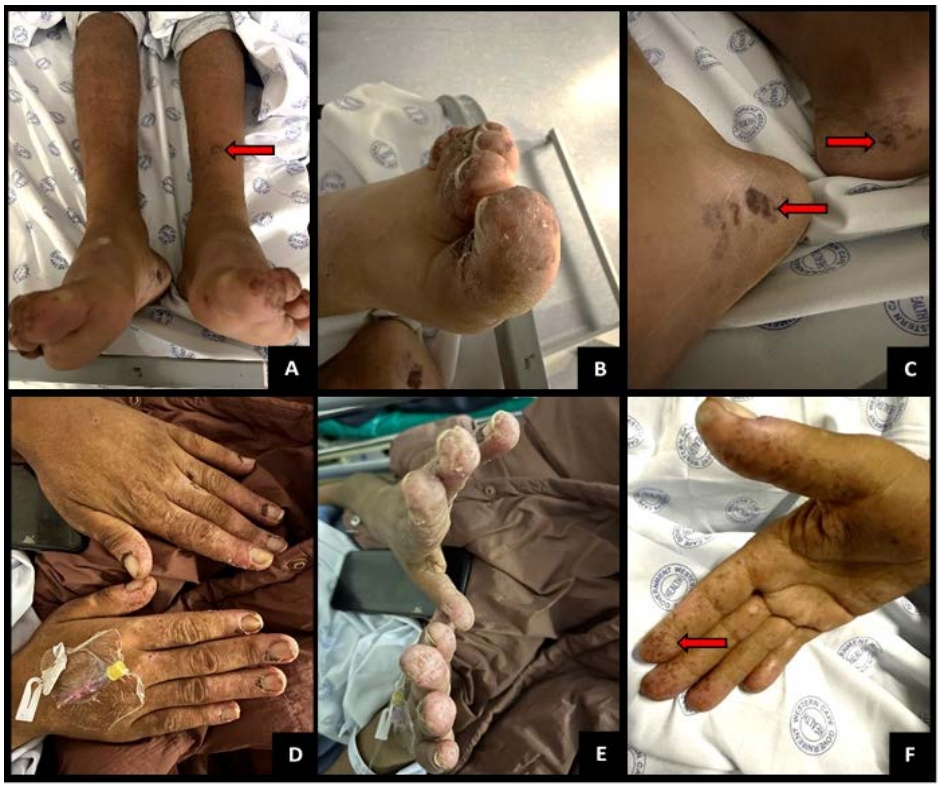

Figure 1: Skin changes on the patient at presentation and on admission.

Case

We report an HIV negative 38-year-old man with a background history of 20 pack-years of tobacco smoking, significant alcohol use, hypertension, and previous drug sensitive pulmonary tuberculosis (PTB) in 2019. It was treated for 6 months with standard TB therapy and complicated by bronchiectasis. He presented in July 2023 with severe abdominal pain, painful swollen hands, feet and legs, a skin rash involving the ears, hands, and feet and shortness of breath.He reported non-specific chest pain with a productive cough in the preceding 8 months prior to presentation to a local hospital where he screened negative for PTB (sputum Gene Xpert and culture negative). A month prior to presentation, he developed painful hands and feet swelling with skin lesions behind the ears. He presented to a hospital with the above symptoms in addition to severe abdominal pain and "red urine". He also reported Raynaud's phenomenon and bilateral lower limb arthralgia.

Clinically he was cachectic, afebrile with healing discoid type lesions on the scalp, healed ulcers on the ear lobes and behind the ears. Abdominal pain was substantial. His oral hygiene was poor with missing teeth and dental caries. He had digital infarcts of both fingers and toes [Figure 1, images B and E) and a vasculitic rash on his nail beds, palms, soles, and legs [Figure 1, images A, C, F]. There was skin desquamation on his fingers, toes, hands, and feet [Image D]. He had bi-pedal oedema. There were bilateral axillary, mobile, < 1 cm non-tender lymph nodes. Hemodynamically, BP was 133/50 mmHg with a tachycardia of 113 bpm and respiratory rate of 25 breaths per minute. Cardiovascular examination was normal and respiratory examination revealed course inspiratory and expiratory crackles.

Table I: Urine porphyrins

Urinary porphyrins fractionation and quantification		
2-COOH (protoporphyrin)	Positive	Trace
4-COOH (coproporphyrin)	Positive	
5-COOH	Positive	
6-COOH	Positive	
7-COOH	Positive	Strongly
8-COOH	Positive	Strongly
Urine Creatinine	29.3 mmol/L	

Table III: Initial baseline investigations

Blood test	Results	Laboratory range
White cell count	8.95 x 10^9 /L	3.92–10.40
Haemoglobin	14.1 x 10^9/L	4.50–5.50
Platelets	204 x 10^9/L	171–388
Sodium	128 mmol/L	135–145 mmol/L
Potassium	4.5 mmol/L	3.5–5.1 mmol/L
Urea	4.1 mmol/L	2.1–7.1 mmol/L
Creatinine	71 umol/L	64–104 umol/L
Calcium	1.91 mmol/L	2.15–2.50 mmol/L
Magnesium	0.73 mmol/L	0.63–1.05 mmol/L
Phosphate	1.09 mmol/L	0.78–1.42 mmol/L
Total bilirubin	6 umol/L	5–21 umol/L
Conjugated bilirubin	2 umol/L	0–3 umol/L
Total protein	68 g/L	60–78 g/L
Albumin	29 g/L	35–52 g/L
ALP	461 U/L	53–128 U/L
GGT	710 U/L	< 68 U/L
ALT	48 U/L	10–40 U/L
AST	101 U/L	15–40 U/L

He had generalised abdominal tenderness but no peritonism. No hepatosplenomegaly or ascites was evident. Neuromuscular examination noted lower limb weakness, globally power reduced to 4/5 bilaterally with difficulty going from a sitting to standing position. He had normal knee and ankle reflexes. No sensory fall-out was evident.

A diagnosis of possible acute porphyria, probably variegate, was made given the history of abdominal pain, ulcerating skin lesions at the ears, urine features, severe abdominal tenderness, lower limb pain and weakness. There was a high index of suspicion for a concomitant autoimmune or connective tissue disease because of the history of Raynaud's phenomena skin rashes and arthralgia and clinical findings of a vasculitic rash and digital infarcts. Initial porphyria and autoimmune screen were done together with other disease-severity determining bedside and laboratory tests.

Table II: Autoimmune screen

Test	Results		Pattern
Anti-Nuclear Antibodies (ANA)	Positive	1 280	Homogenous Pattern
Anti-double stranded DNA	Positive	149 IU/mL	
Anti-Smith Antibody	Positive	28.2 IU/mL	
Anti-RNP Antibody	Positive	38.4 IU/L	
Anti-proteinase 3	Negative		
Anti-myeloperoxidase	Negative		
Anti-cardiolipin (IgG, IgM)	Negative		
Anti B2-Glycoprotein	Negative		
Lupus anticoagulant	Negative		
Anti-smooth muscle antibody	Negative		
Anti LKM 1 antibody	Negative		
Complement C3	0.39 g/L	0.9–1.80	
Complement C4	0.05 g/L	0.1–0.4	
Total IgG	30.73 g/L	7–16	
Urine protein:creatinine ratio	0.6 g/day		

Table V: Blood tests at three months post discharge

Blood test	Results	Laboratory range
White Blood Cells	5.58 x 10^9 /L	3.92–10.40
Haemoglobin	12.7 x 10^9 /L	4.50–5.50
Platelets	188 x 10^9/L	171–388
Sodium	140 mmol/L	135–145 mmol/L
Potassium	3.4 mmol/L	3.5–5.1 mmol/L
Urea	3.2 mmol/L	2.1–7.1 mmol/L
Creatinine	65 umol/L	64–104 umol/L
Calcium	2.10 mmol/L	2.15–2.50 mmol/L
Magnesium	0.77 mmol/L	0.63–1.05 mmol/L
Phosphate	1.16 mmol/L	0.78–1.42 mmol/L
Total bilirubin	4 umol/L	5–21 umol/L
Conjugated bilirubin	2 umol/L	0–3 umol/L
Albumin	36 g/L	35–52 g/L
ALP	106 U/L	53–128 U/L
GGT	368 U/L	< 68 U/L
ALT	26 U/L	10–40 U/L
AST	27 U/L	15–40 U/L

Table IV: Arterial Blood Gases

PH	7.44	7.350–7.450
PO2	8.78 kPa	11.1–14.4
PCO2	5.01 kPa	4.67–6.00
Bicarbonate	25.8 mEq/L	20.0

Bedside urinary porphyrin screen was positive (Figure 2, Picture 1) and qualitative laboratory urinary porphobilinogen and urinary porphyrins were positive. Further light-shielded urine sent to the laboratory for urinary porphyrin fractionation and quantification showed positive porphyrins as shown in table I.

R59W mutation analysis for the common mutation causing VP in South Africa, was negative. The autoimmune screen was positive for several autoimmune antibodies (Table II).

He had hypocomplementemia, proteinuria and elevated total IgG level as shown above. He was hyponatremic with an abnormal liver profile (Table III).

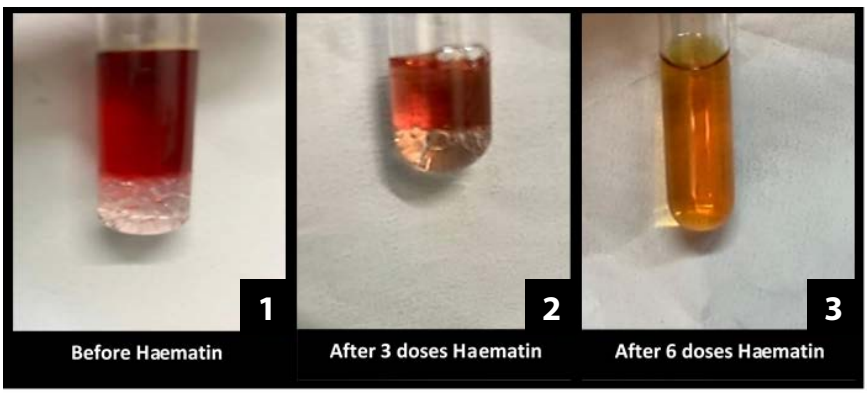

Figure 2: Patient's urine changes at presentation, during treatment, and at the end of AIP treatment (Watson-Schwartz test)

His coagulation was preserved, INR 0.94, and he had elevated C-reactive protein, 95 mg/L, and an elevated Ferritin of 1182 ug/L in keeping with a marked inflammatory response.

Viral hepatitis markers were negative (Hep A IgM, Hep BsAg and Hep C antibody). The sepsis screen (sputum, blood, and urine cultures) was negative, with a negative repeat sputum GeneXpert MTB/Rif ultra-assay. The patient was treated for an acute porphyric attack with IV haem arginate (5 ml in 100 ml of 20% albumin intravenously) daily for 6 days, intravenous dextrose saline solution, IV opioids, and a high-energy diet. After initiating haem arginate, his abdominal pain resolved. Urine porphyrin activity settled on day 6 (Figure 2, picture 3). Further investigation included a normal ECG; and an echocardiogram demonstrating a non-dilated left ventricle with mildly reduced systolic function (ejection fraction of 45–50%) with no valvular pathologies noted. The right ventricle was normal in size and function. Skin biopsy of the vasculitic rash demonstrated small vessel vasculitis as well as increased dermal mucopolysaccharide deposition (Figure 3).

Given his history of cough, and shortness of breath on minimal exertion with oxygen saturation of 92% on room air, an arterial blood gas, chest radiograph and a CT pulmonary angiogram (CTPA) were done to investigate for lung infection and/or pulmonary embolism. Blood gas on ambient air demonstrated type 1 respiratory failure (Table IV).

The chest radiograph demonstrated background chronic lung disease with superimposed pneumonia and an incidental finding of a right shoulder internal fixation which retrospectively was reported to be a fracture following a motor vehicle accident (Figure 4) . The CTPA was negative for pulmonary embolism but noted bilateral pleural effusions with compressive atelectasis and bilateral upper lobe cicatricial bronchiectasis with fibrosis and subpleural tethering, which the pulmonology team assessed as post-TB bronchiectasis. A renal biopsy was performed because of the proteinuria indicated the International Society of Nephrology/Renal Pathology Society class II lupus Nephritis (Figure 5). In conjunction with the acute porphyria, a diagnosis of systemic lupus erythematosus with associated class 2 lupus nephritis and small vessel vasculitis was made, and the patient was started on oral steroids (Prednisone 40 mg daily), an immunomodulator (Azathioprine 50 mg daily) and chloroquine (250 mg Monday-Friday). The abdominal pain resolved. Skin and joint symptoms slowly resolved.

At a 3-month post-discharge review, there was marked clinical improvement. Follow-up blood tests are listed. His liver profile normalised, although GGT remained elevated. His liver synthetic function was restored with normal serum albumin and INR (Table V).

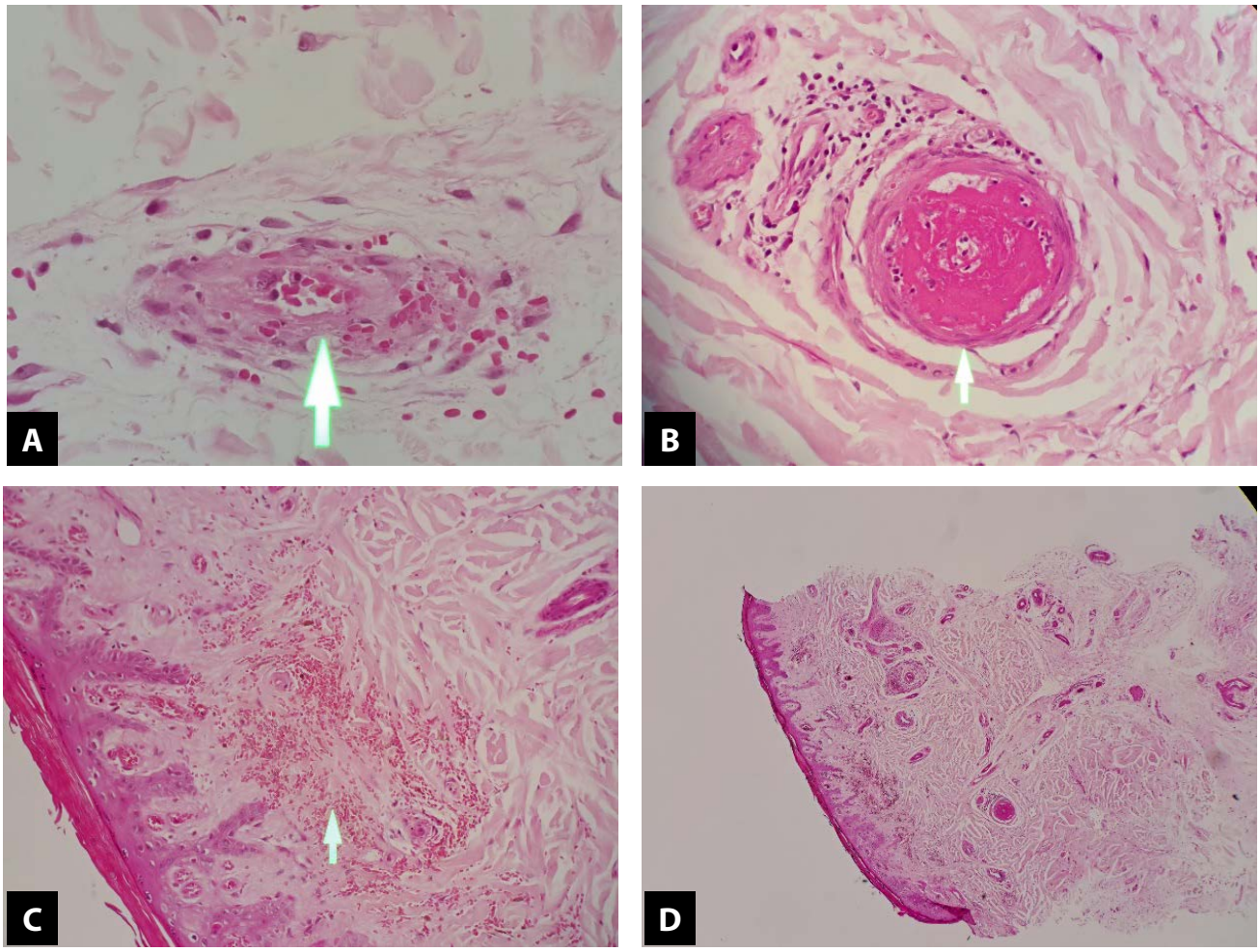

Figure 3: Skin biopsies (A (H&E sections 400x objective magnification): Early fibrinoid necrosis; B (H&E sections 400x objective magnification): Fibrinoid necrosis with fibrin thrombus; C (H&E section at 100x objective magnification): Red blood cell extravasation, D (H&E section at 40x objective magnification): Low power view)

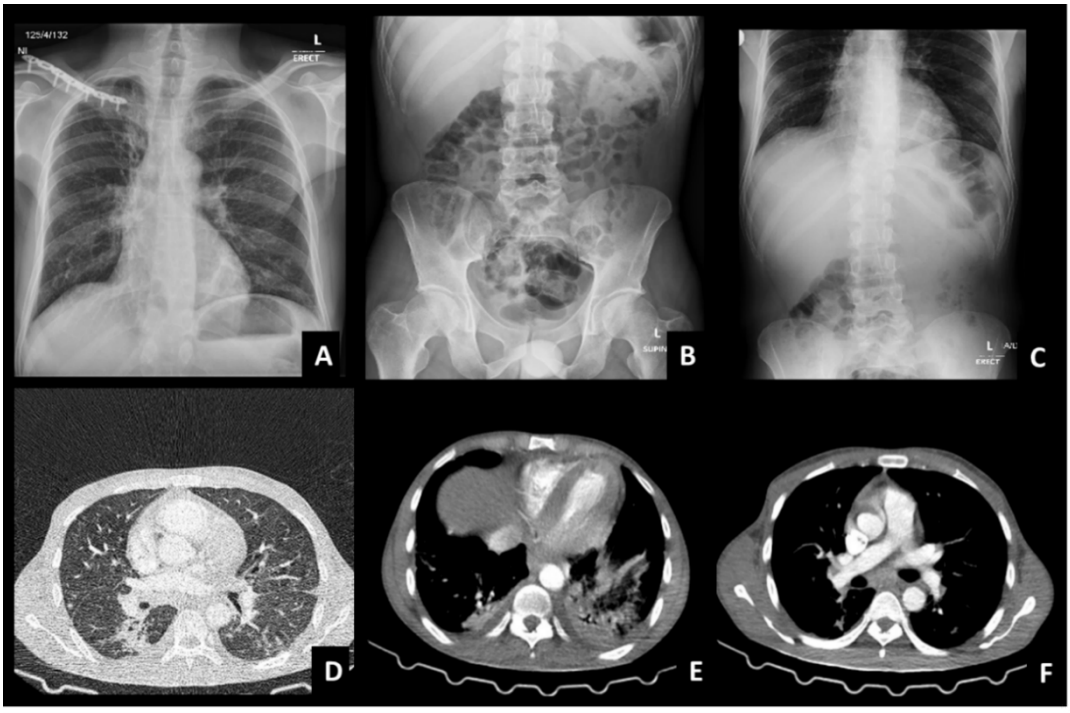

Figure 4: Radiological Imaging

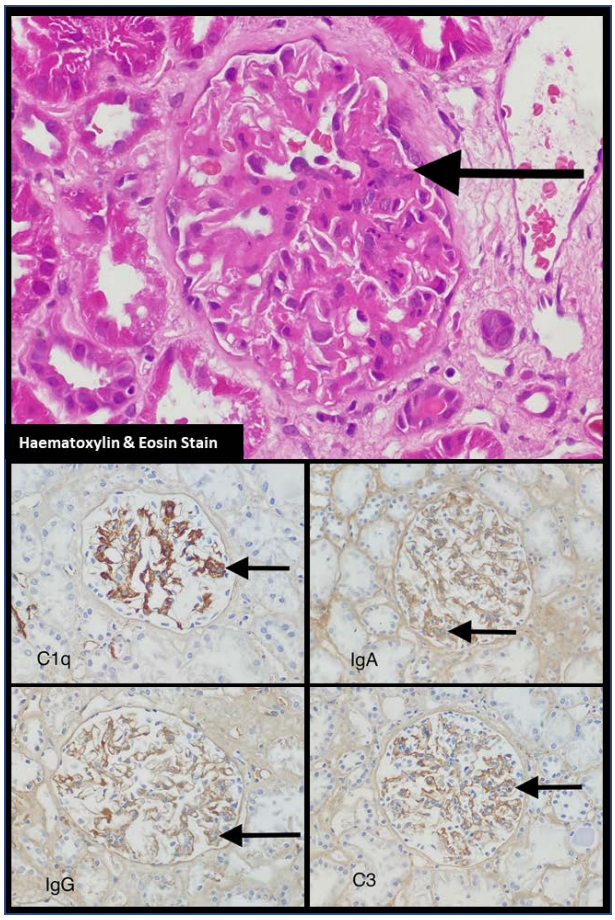

Figure 5: Renal biopsy (All images are at 400x magnification. Black arrows show areas of mesangial hypercellularity)

Discussion

AHP and SLE are rare diseases. Their co-existence is very rare. For example, in Europe, the prevalence of symptomatic AHP is estimated to be 0.5 cases per 100 000 population[7] while that of SLE is 6.5 to 85 per 100 000 population.[8] As of June 2023, there have been 16 cases of AHP-SLE co-existence reported.[6] Both diseases had diagnostic confirmation. Response to therapy was good with haem-arginate as part of the management of acute porphyria and steroids, chloroquine, and azathioprine for SLE management. Most patients in previously reported case reports were female (13 out of the 16), and no case has previously been reported in South Africa.[6] Drugs, reported in 37% of patients, are the most frequent trigger of acute attacks of porphyria.[9,10] The putative mechanisms for co-existence invariably are medications used in SLE. In our patient, medications were only started after diagnosis of SLE. Equally, previous TB treatment would have been highly provocative for initiating an acute attack. This did not occur, and inexplicably, the patient reported no abdominal pain or other symptoms while on anti-TB therapy. The use of alcohol by the patient, similarly, would also be evocative of an acute attack of porphyria. This also was not observed even though his liver profile, an elevated GGT, may have suggested ongoing chronic alcohol use. This may support that the advent of clinical SLE evoked the phenotypic expression of acute porphyria. How lupus triggers porphyria is unknown. The patient did develop sepsis of the skin lesions, which may have been a trigger. The patient was nutritionally depleted, and a scenario of a "perfect storm" where multiple factors–sepsis, marked inflammation, carbohydrate depletion–all coalesced to trigger an acute attack of porphyria for the first time. The issue of whether SLE was potentiated by the acute porphyria is a moot point.

Conclusion

Concomitant acute porphyria and SLE are documented, albeit rare, phenomena. In this instance AIP an acute porphyria was triggered by an SLE flare. A high index of suspicion with careful diagnostics is required. The reasons underlying how the 2 conditions interplay with each other are unclear. In our patient, the SLE seemingly was the evocative trigger for an acute porphyria attack.

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