Case 1

- 18 yo woman came to ER with a 5-day history of severe abdominal pain
- Localized, intermittent, sharp, epigastric and periumbilical pain associated with mild nausea but no vomiting for the past 6 months / pain usually starting prior to the beginning of a menstrual cycle, lasting for the length of the cycle
- Discoloration of urine during the episodes
- PMH: 2 previous hospital admissions for hyponatremia work-up

- PMH: spells of confusion with indeterminate jerking spasms of the upper extremities and facial muscles
- No sensitivity to the sun
- PE: mild tenderness on deep palpation of the abdomen / tachycardia / symmetrical motor weakness of the arms
- Stools were heme (-)
- Na: 132 mEq/L (135-145 mEq/L)

- Clinical diagnosis?

    - AIP (Acute Intermittent Porphyria)

What are porphyrias?

- Rare, inherited or acquired diseases resulting from enzyme deficiencies that lead to heme pathway intermediates accumulation
- Inheritance pattern for most of them is AD with variable penetrance – majority of affected persons do not exhibit clinical disease
- ♀ >♂
- Identification of the defect is important for providing genetic counselling / advice on how to avoid precipitating factors

Anatomical classification of porphyrias

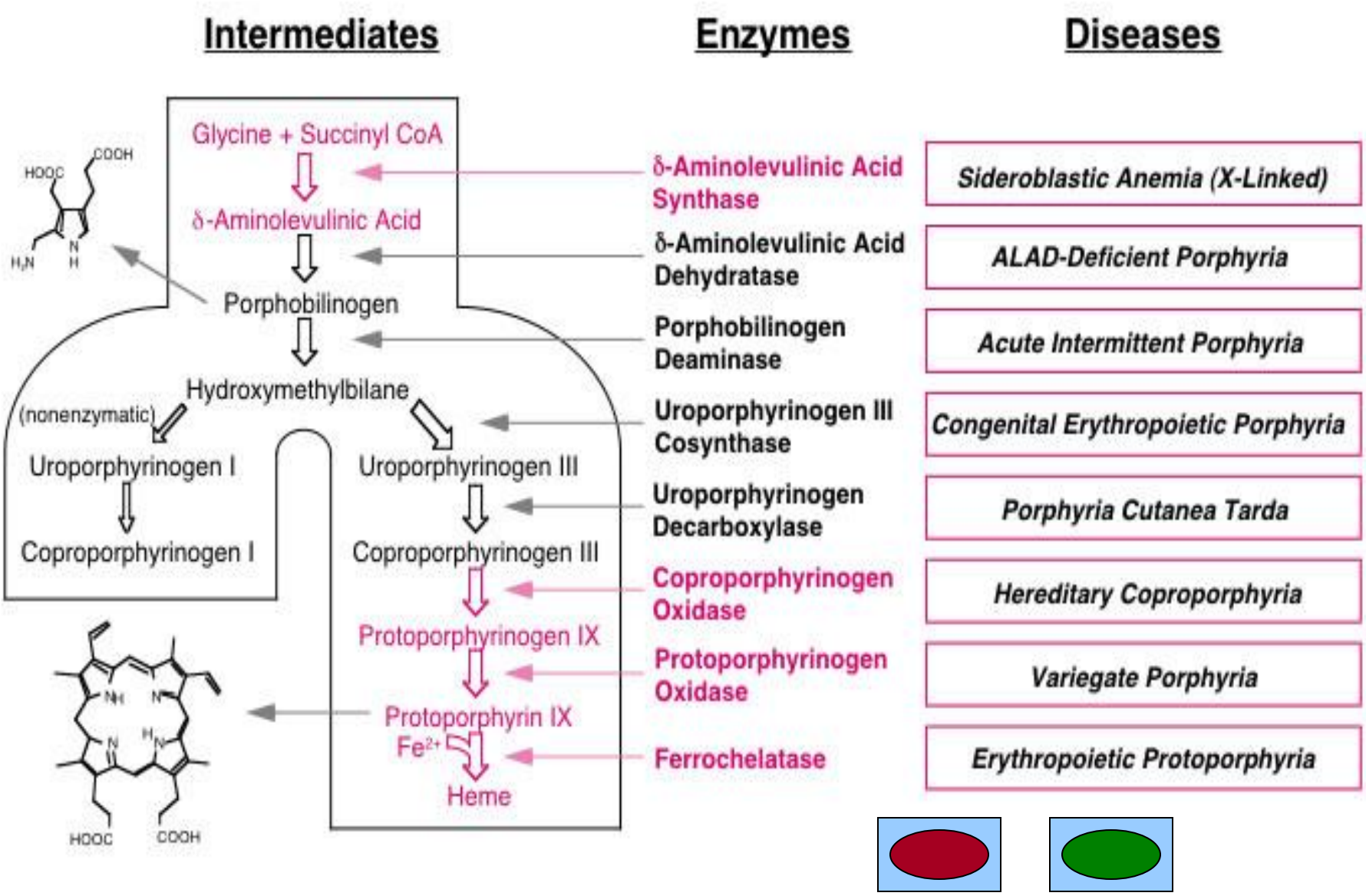
- **Hepatic:**
  - Intermitent Acute Porphyria (IAP)
  - Hereditary Coproporphyria (HCP)
  - Variegate Porphyria (VP)
  - Porphyria Cutanea Tarda (PCT)
- **Erythropoietic:**
  - Congenital Erythropoietic Porphyria (CEP)
  - Erythropoietic Protoporphyria (EPP)

Clinical Classification of Porphyrias

- Acute Porphyrias (neurological)
- Non-Acute Porphyrias (skin photosensitivity)

Acute Intermitent Porphyria
Variegate Porphyria
Hereditary Coproporphyria

Porphyria Cutanea Tarda
Erythropoietic Protoporphyria
Congenital Erythropoietic Porphyria


Intermediates
Enzymes
Diseases
Glycine + Succinyl CoA
δ-Aminolevulinic Acid
Porphobilinogen
Hydroxymethylbilane
(nonenzymatic)
Uroporphyrinogen I
Uroporphyrinogen III
Coproporphyrinogen I
Coproporphyrinogen III
Protoporphyrinogen IX
Protoporphyrin IX
Fe2+
Heme
δ-Aminolevulinic Acid Synthase
δ-Aminolevulinic Acid Dehydratase
Porphobilinogen Deaminase
Uroporphyrinogen III Cosynthase
Uroporphyrinogen Decarboxylase
Coproporphyrinogen Oxidase
Protoporphyrinogen Oxidase
Ferrochelatase
Sideroblastic Anemia (X-Linked)
ALAD-Deficient Porphyria
Acute Intermittent Porphyria
Congenital Erythropoietic Porphyria
Porphyria Cutanea Tarda
Hereditary Coproporphyria
Variegate Porphyria
Erythropoietic Protoporphyria

Laboratory Measurements in the Case Patient

Substance measured	Result
Porphobilinogen (urine)	95 µmol/L (0-8.8 µmol/L)
	* excludes lead poisoning
5- Aminolevulinic acid (urine)	724 µmol/L (0-35 µmol/L)
Porphobilinogen deaminase (erythrocytes)	2 mU/g (2.1-4.3 mU/g)

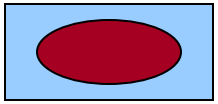
How should I work-up this case?

Step 1: Is this an acute (neurological) case or a non-acute (cutaneous) case?

Acute case

Step 2: Qualitative PBG urine screening test (Hoesch test- Ehrlich's reagent -or Watson-Schwartz test)

Magenta color → (+) → quantitative assay



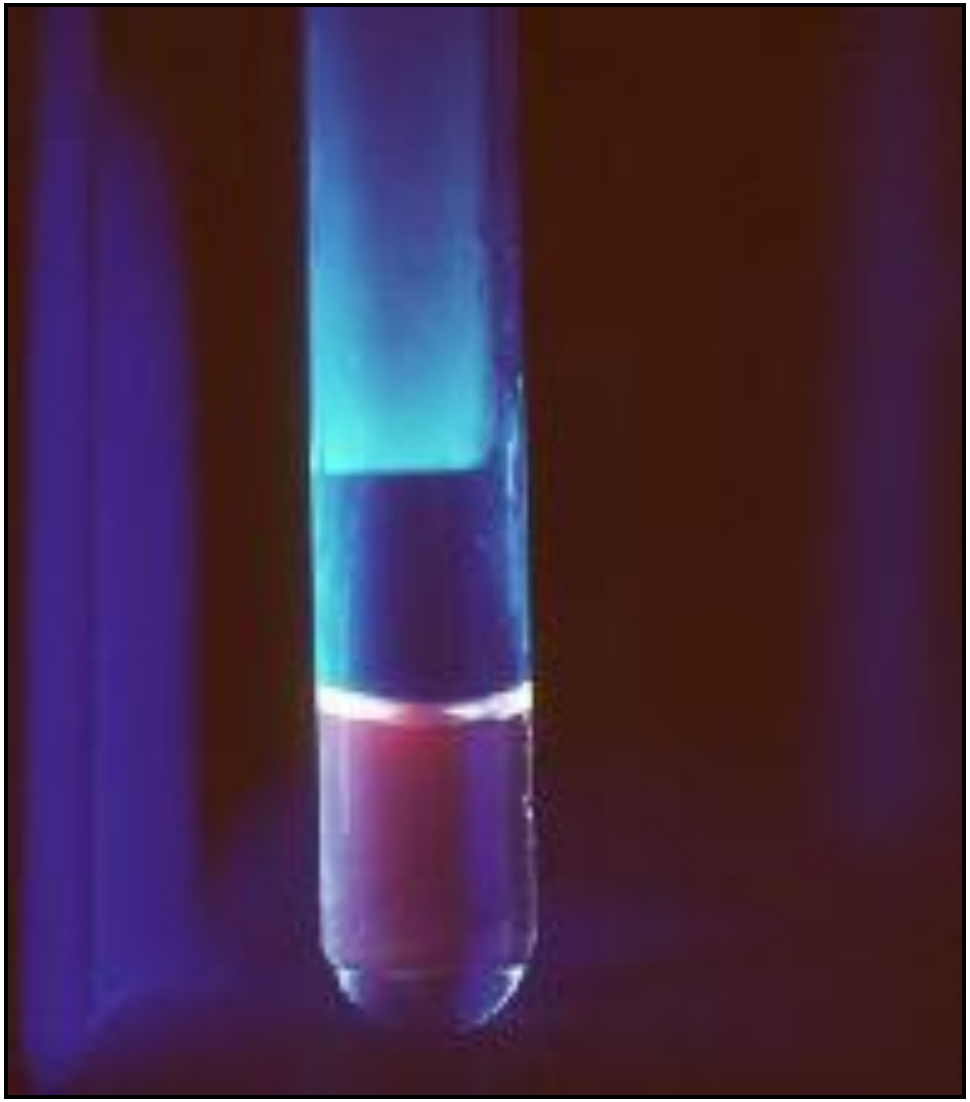
Step 3: Fecal Porphyrin Screening test

Negative (AIP) Positive (VP or HCP)

Case explanation

- Severe abdominal pain (80%),confusion, jerking spasms – ALA and PBG (neurotoxins) accumulate in tissues → acute neurovisceral symptoms
- Tachycardia (80%) - release of catecholamines during attack /sudden death
- Menstrual cycle – estrogen is a precipitating factor
- Discoloration of urine – accumulation of fluorescent porphyrins
- Hyponatremia – inappropriate secretion of antidiuretic hormone

- Urine (early morning): - 20°C
- Feces: - 20°C
- Whole blood: 4°C
- Erythrocytes: - 20°C
- Plasma: - 20°C



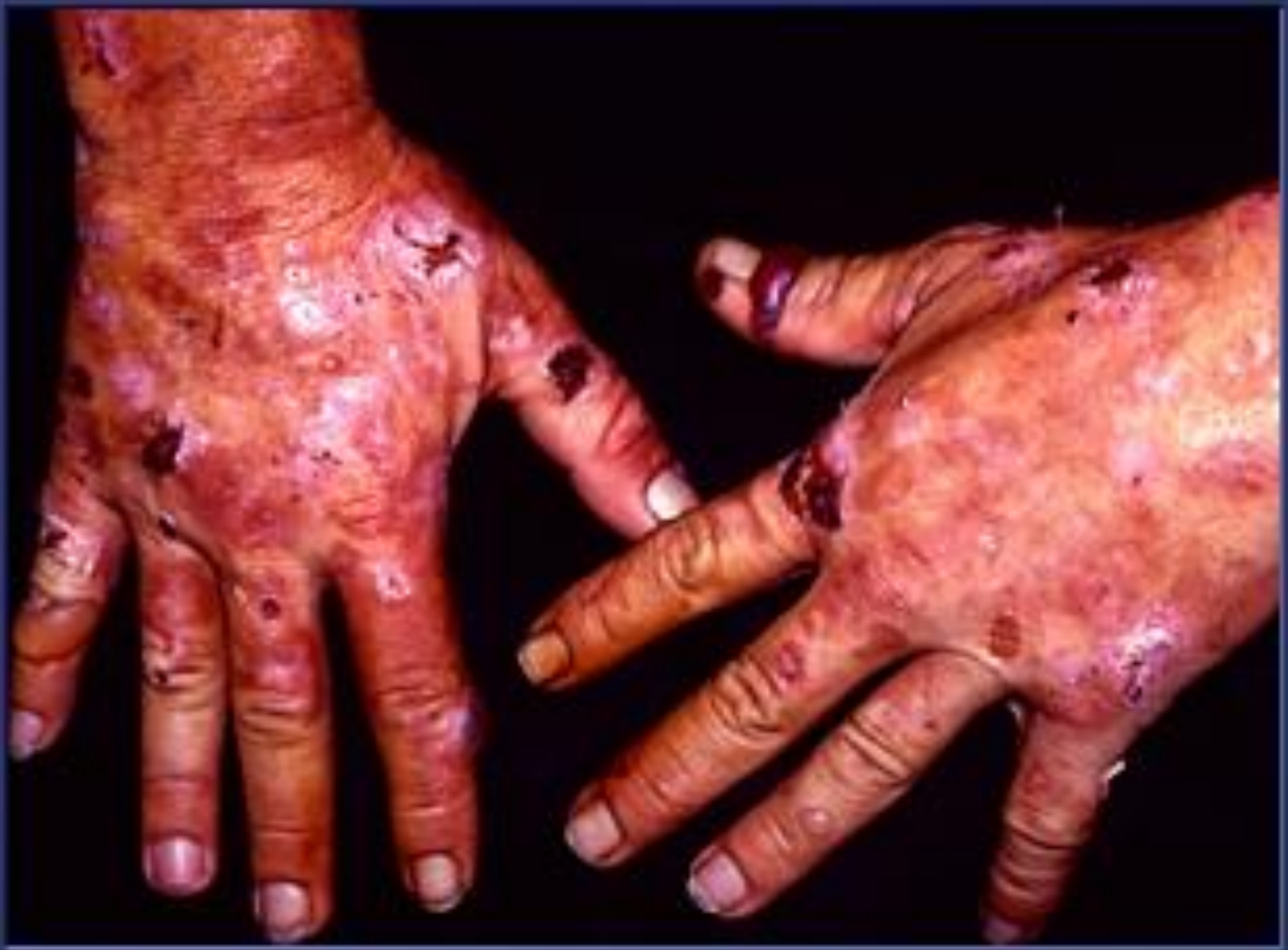
Subsequent Hospital Course

- Treatment: oral analgesics, antiemetics, intravenous administration of dextrose and hematin (cimetidine is another option)

- Placed on high-carbohydrate diet, instructed to avoid long periods without eating and to use medications only after consulting physician

Case 2

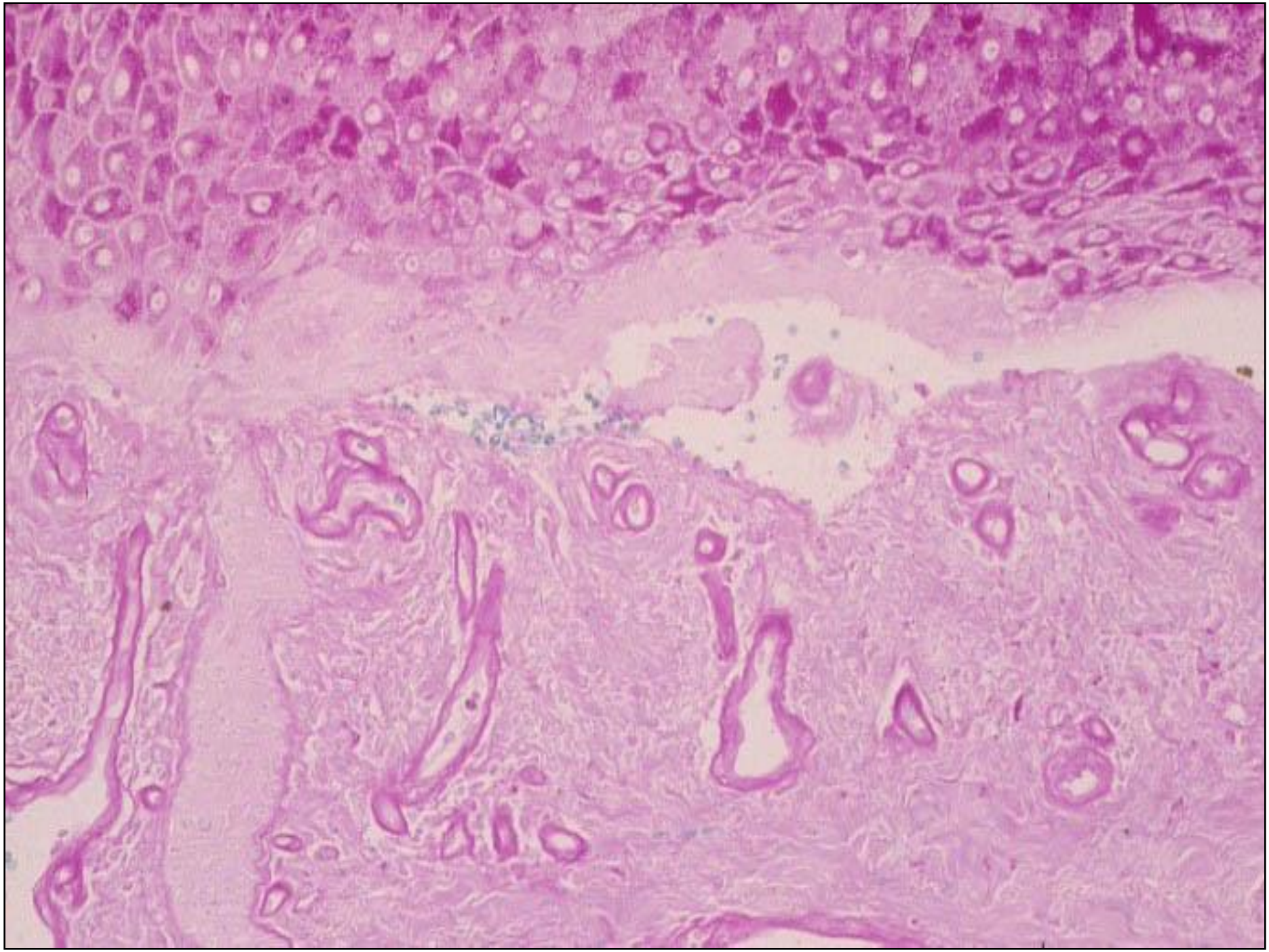
- 40 yo landscaper presents with painful blisters on the back of his hands shortly after the landscaping season began
- Discoloration of urine
- Denied any recent exposure to new soaps, detergents or medications
- PMH: partial complex seizure disorder that begun 3 years after head trauma (taking phenytoin)
- Average weekly ethanol intake: 18 12-oz cans of beer
- PE: besides the blisters, was noted to have hypertrichosis

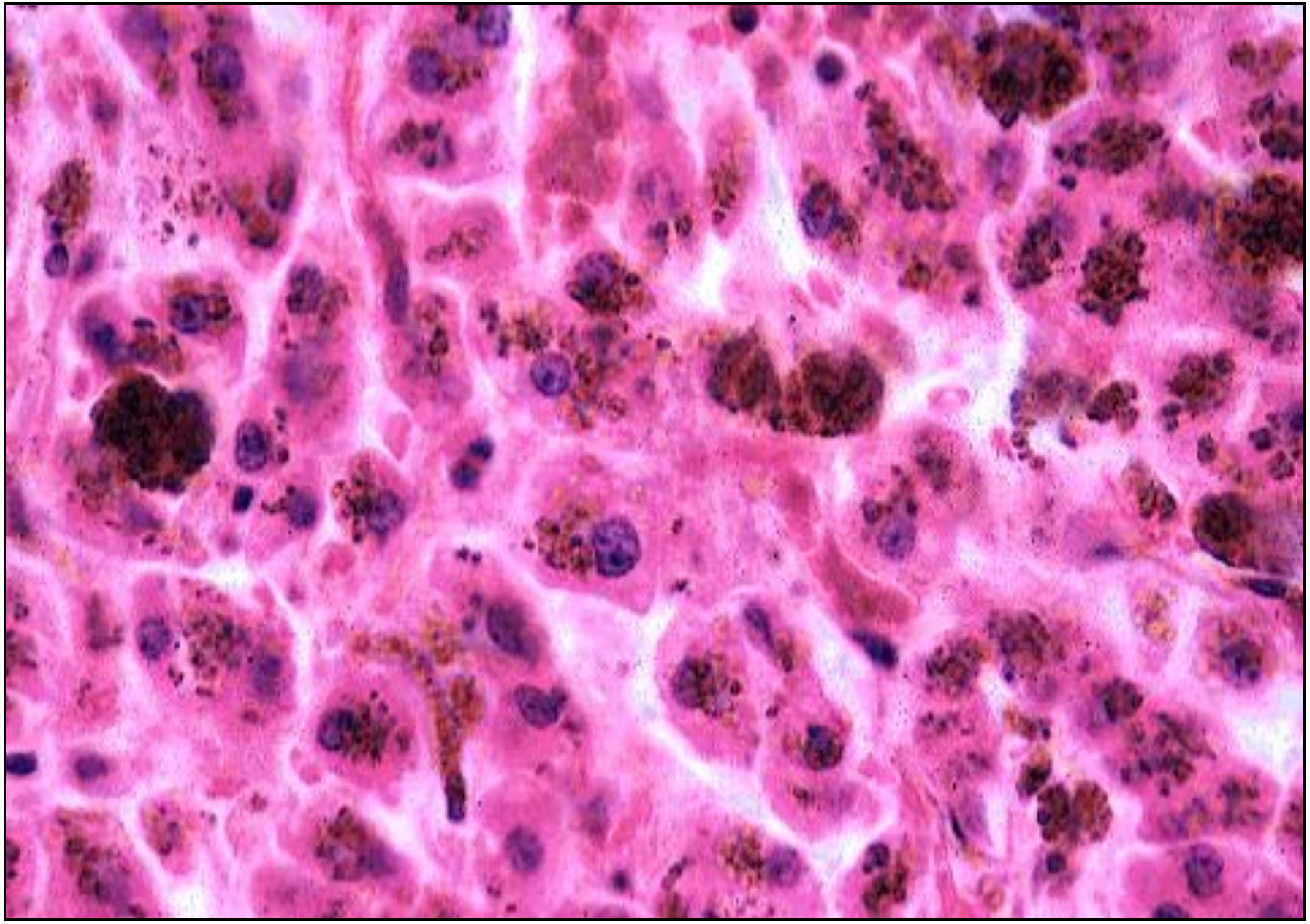


Laboratory Measurements in the Case Patient

- Fasting Glucose: 159 mg/dL (70-105 mg/dL)
- Alanine aminotransferase:135 U/L (<45 U/L)
- Aspartate aminotransferase:100 U/L (<41 U/L)
- Alkaline phosphatase: 161 U/L (30-115 U/L)
- Ferritin: 989 ng/mL (19-260 ng/mL)

- Clinical diagnosis?
  - Bullous pemphigoid
  - Herpetic infections
  - Staphylococcal infections
  - Contact dermatitis
  - Chemical burns
  - Pemphigus vulgaris
  - Porphyria Cutanea Tarda (type I – sporadic)





24-hour urine collection

- Uroporphyrin: 1000 μg (<27)
- 5-carboxyporphyrin: 120 (<5)
- 6-carboxyporphyrin: 120 (<3)
- 7-carboxyporphyrin: 720 (<6)
- Coproporphyrin: 67 (<72)

- HCV antibody (+) – active disease confirmed – viral load of more than 1 milion particles of RNA by PCR

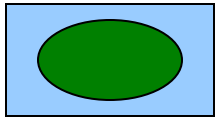
How should I work-up this case?

Step 1: Is this an acute (neurological) case or a non-acute (cutaneous) case?

Cutaneous case

Step 2: Urine porphyrin screening test (qualitative)

Positive (now you have to quantify)



Step 3: ↑ Uro (PCT) ↑ Copro (VP, HCP)

Step 4: Free Erythrocyte Protoporphyrin

Normal (PCT) ↑ (Erythropoietic Protoporphyria)

Case explanation

- Painful blisters – ultraviolet light transforms (oxidizes) accumulated porphyrins in the skin into toxins that cause skin fragility

- Hypertrichosis - hair bulb keratinocytes are activated by the dual action of light and porphyrins

- Alcohol - induces ALA synthase, the first enzyme in heme biosynthesis, and inhibits the latter enzymes such as ferrochelatase

- HCV (also HIV) – triggering factors /specific anticytosolic antibodies are associated with liver damage

- Hepatic iron overload (siderosis) - present in nearly every case of PCT /↑ iron, ferritin, transferrin saturation, ↓ TIBC

- Diabetes mellitus - present in 15-20% of PCT patients.

Subsequent clinical course

- Instructed to avoid exposure to direct sunlight, avoid ethanol, and other precipitating drugs (such as phenitoin). Switched to Gabapentin

- Removal of one unit of blood with phlebotomy weekly or biweekly to reduce iron levels

- Antimalarial agent (hydroxychloroquine or chloroquine) biweekly (antimalarials complex with porphyrin and promote the excretion into bile)