

# A case report on variegate porphyria after etonogestrel placement



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## INTRODUCTION

Variegate porphyria (VP) is a rare disorder of heme synthesis caused by an autosomal dominant trait, partial deficiency in the protoporphyrinogen oxidase (PPOX) gene.<sup>1</sup> It is characterized by acute attacks of neurovisceral symptoms—behavioral changes and abdominal pain—as well as cutaneous photosensitivity manifesting as skin fragility and blistering.<sup>2</sup> Women are more likely to be symptomatic; skin symptoms typically develop in the second decade of life.<sup>1</sup> Pertinently, many patients remain asymptomatic throughout their lives, while some patients present with either neurovisceral symptoms, photosensitivity, or both.<sup>2</sup> It has a worldwide distribution but has an especially high frequency in South Africa.<sup>1</sup> We report a teenage woman who presented with cutaneous VP after etonogestrel implant (Nexplanon) placement—a progestin-only contraceptive.

## CASE REPORT

An 18-year-old woman, with a nonsignificant past medical history, presented with multiple erythematous, crusted, eroded papules on the dorsal aspects of the hands, as well as several lesions on the face. The lesions were painful, pruritic, nonhemorrhagic, and had been present for 1 month. The rash was initially thought to be consistent with impetigo, and she was prescribed mupirocin ointment to apply to affected regions. Over the ensuing month, existing lesions partially improved, but did not resolve; she developed new lesions on the face and crusting of the eyelids.

At a subsequent visit 1 month later, she continued to have round macules on the dorsal aspects of the

### Abbreviations used:

Ig: immunoglobulin  
PPOX: protoporphyrinogen oxidase  
VP: variegate porphyria



**Fig 1.** On initial presentation, the patient demonstrated bilateral painful and pruritic erythematous crusted and eroded papules, ultimately found to be consistent with a cutaneous variegate porphyria flare.

hands and involvement of the nasal bridge (Fig 1). Based on the persistence of symptoms, the differential diagnosis was expanded to include porphyria and pseudoporphyria. Triggers were explored, and it was noted that she had an etonogestrel implant placed 4 months prior to presentation. This was the first time the patient had been on hormonal birth

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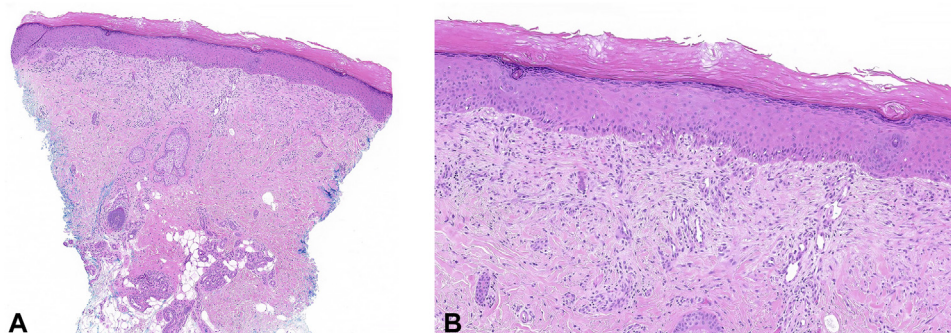
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**Fig 2.** **A**, Low-power view of the biopsy revealed normal epidermis with superficial dermal fibrosis. There was also a sparse superficial dermal perivascular lymphocytic infiltrate (Hematoxylin-eosin stain; original magnification:  $\times 40$ ). **B**, On higher-power view, scattered foci of microhemorrhage and angioplasia were observed (Hematoxylin-eosin stain; original magnification:  $\times 100$ ).

**Table I.** The patient’s laboratory test values that are consistent with variegate porphyria. Erythrocyte porphobilinogen deaminase activity was normal at 7.7 nmol/L/sec (reference value,  $\geq 7.0$  nmol/L/sec), and erythrocyte aminolevulinic acid dehydratase activity was normal at 4.9 nmol/L/sec (reference value,  $\geq 4.0$  nmol/L/sec)

Urinary porphyrins	Reference value	Case values
Porphobilinogen	$\leq 2.2$ mcmol/24h	69.3*
Coproporphyrin (tetra)	$\leq 168$ nmol/24h	1260*
Pentacarboxylporphyrins	$\leq 10$ nmol/24h	134*
Hexacarboxylporphyrins	$\leq 8$ nmol/24h	29*
Heptacarboxylporphyrins	$\leq 9$ nmol/24h	21*
Uroporphyrin (octa)	$\leq 30$ nmol/24h	61*
Fecal porphyrins	Reference value	Case values
Coproporphyrin I and III	$< 500$ and $< 400$ mcg/24h, respectively	1611* + 7675*, respectively
Coproporphyrin III/I ratio	$< 1.2$	4.76*
Protoporphyrin	$< 1500$ mcg/24h	14134*
Isocoproporphyrin	$< 200$ mcg/24h	1076*
Isoheptacarboxyl	$< 30$ mcg/24h	32*
Pentacarboxyl I and III	$< 20$ mcg/24h	41* + 92*, respectively
Isopentacarboxyl	$< 80$ mcg/24h	166*
Uroporphyrin I and III	$< 120$ and $< 50$ mcg/24h, respectively	32 + 8, respectively
Heptacarboxyl I and III	$< 40$ mcg/24h	2 + $< 1$ , respectively
Hexacarboxyl I and III	$< 10$ mcg/24h	3 + 5, respectively
Plasma porphyrins	Reference value	Case values
Uroporphyrin	$\leq 1.0$ mcg/dL	$\leq 1.0$
Heptacarboxylporphyrins	$\leq 1.0$ mcg/dL	$\leq 1.0$
Hexacarboxylporphyrins	$\leq 1.0$ mcg/dL	$\leq 1.0$
Pentacarboxylporphyrins	$\leq 1.0$ mcg/dL	$\leq 1.0$
Coproporphyrin	$\leq 1.0$ mcg/dL	$\leq 1.0$
Protoporphyrin	$\leq 1.0$ mcg/dL	1.9*

\*Elevated value.

control; it was implanted several weeks prior to the onset of symptoms.

Punch biopsies of 2 lesions on the dorsal aspect of the hand demonstrated largely normal acral-site epidermis with superficial dermal fibrosis, reactive

angioplasia, scattered foci of microhemorrhage, and sparse perivascular lymphocytic infiltrate (Fig 2). Direct immunofluorescence studies revealed smooth IgG, IgA (weak), immunoglobulin M (IgM) (weak), and C3 binding in the superficial vessel walls.

Additionally, weak linear IgG deposition was observed along the dermoepidermal junction. Direct immunofluorescence results were compatible with a porphyria immune deposition pattern. In combination, the histologic features were consistent with reparative changes in the setting of porphyria. Laboratory values confirming the diagnosis of VP are shown in [Table I](#). Genetic testing with the Invitae Comprehensive Porphyrins Panel showed a heterozygous variant of uncertain significance in the PPOX gene (variant c.23T>C [p.Leu8Pro]).

She denied any acute porphyria symptoms, such as abdominal pain, neuropathy, nausea, or confusion. While *de novo* variants are very rare, she has no known family history of porphyria and denies South African ancestry; she has Russian Jewish ancestry. Due to the timeline of her cutaneous flare several weeks after etonogestrel implant placement, this was thought to be the trigger for her symptoms. She had the etonogestrel implant removed; over the ensuing month, she reported substantial improvement in her cutaneous symptoms, with minimal crusting and a decrease in size of lesions. She also used topical azelaic acid 10% in a cream vehicle with improvement in postinflammatory hyperpigmentation.

## DISCUSSION

VP is a rare autosomal dominant disorder of the seventh step of heme synthesis caused by a mutation in the PPOX gene.<sup>3</sup> Heme precursors build up in the liver, causing hepatic porphyria.<sup>1</sup> There are 2 manifestations of disease: Acute neurovisceral attacks and cutaneous photosensitivity. Acute symptoms are characterized by behavioral changes, neuropathy, and abdominal pain.<sup>2</sup> Skin symptoms often occur independently of neurovisceral attacks and are caused by a buildup of the PPOX substrate—protoporphyrinogen—in the skin, causing fragility and blistering in sun-exposed

areas.<sup>3</sup> It is diagnosed by plasma fluorescence with an emission peak at 626 nm. Patients have elevated fecal protoporphyrins and coproporphyrins, as well as elevated urine delta-aminolevulinic acid, porphobilinogen, and coproporphyrins and uroporphyrins.<sup>1</sup>

It has been shown that stress, infection, fasting, and drugs that induce cytochrome P-450 enzymes trigger VP exacerbations.<sup>4</sup> Additionally, sex steroids—particularly progesterone—are inducers of heme synthesis and can provoke porphyria symptoms in women. Cyclical acute porphyria attacks have been reported during the luteal phase of the menstrual cycle, when progesterone is particularly elevated.<sup>4,5</sup> To the authors' knowledge, this is the first report of cutaneous VP triggered by progesterone-only Nexplanon implantation.

## Conflicts of interest

None disclosed.

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