OLGU SUNUMU CASE REPORT

DOI: 10.5336/intermed.2022-92361

A Delayed Diagnosis of Variegate Porphyria, Seen with Verrucous Carcinoma

Verrüköz Karsinom ile Görülen Geç Teşhis Edilen Variegate Porfiri

Çağdaş KAYA[a], Ayli HEYDARİ[a], İlayda ALTUN[a], Sude ÇAVDAROĞLU[a], Gülbüz SEZGİN[b]

[a]Maltepe University Faculty of Medicine, İstanbul, Türkiye
[b]Division of Internal Medicine, Maltepe University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT Variegate porphyria (VP) is an autosomal dominant porphyria characterized by both cutaneous and neurovisceral symptoms. In this case we discuss a 65-year-old female patient with bullous lesions on hands, lethargy, increased facial hair and darkened facial skin. A form of acute porphyria, VP is caused by mutations in PPOX, a gene that carries instructions for making an enzyme called protoporphyrinogen oxidase. Here, we report a heterozygous mutation of the PPOX gene in a Turkish female VP patient who has been diagnosed with chronic renal failure secondary to porphyria. Porphyria is one of those disease needed to be kept in mind as differential diagnosis. Late diagnosis of this disease would lead to different chronic organ failures as a result of heme accumulation in different tissues and organs. This case, it is a clear reminder for the health care workers to remember the "Primum non no nonocere" rule and also remembering porphyria as a differential diagnosis in longterm attacks and symptoms.

Keywords: Heme; porphyria; chronic renal failure; variegate porphyria; verrucous carcinoma

ÖZET Variegate porfiri (VP), hem kutanöz hem de nöroviseral semptomlarla karakterize otozomal dominant bir porfiridir. Bu olguda, ellerde büllöz lezyonlar, uyuşukluk, yüzde kıllanma ve yüz derisinin koyulaşması olan 65 yaşında bir kadın hastayı tartışıyoruz. Akut porfirinin bir formu olan VP'ye, protoporfirinojen oksidaz adı verilen bir enzim yapmak için talimatlar taşıyan bir gen olan PPOX'taki mutasyonlar neden olur. Burada, porfiriye sekonder kronik böbrek yetersizliği tanısı almış bir Türk VP tanılı hasta sunuyoruz. Bu hastanın PPOX geninde heterozigot bir mutasyon ispatlanmıştır. Porfiri, ayırıcı tanıda akılda tutulması gereken hastalıklardan biridir. Bu hastalığın geç teşhisi, farklı doku ve organlarda hem birikimi sonucunda farklı kronik organ yetersizliğine yol açacaktır. Bu vakada, uzun dönem komplikasyonları beraberinde getiren ataklardan kaçınmak için ayırıcı tanıda porfirinin akılda tutulması gerektiğinin açık bir hatırlatıcısıdır ve "Primum non nocere" ilkesine uymak için sağlık çalışanlarının daha fazla eğitilmesi kritik önem taşımaktadır.

Anahtar Kelimeler: Hem; porfiri; kronik böbrek yetersizliği; variegate porfiri; verrüköz kanser

Porphyrias are composed of group of diseases which define a dysfunction in heme synthesis pathway resulting in accumulation of porphyrin precursors.[1] Variegate porphyria (VP) is an autosomal dominantly inherited disease occurring in consequence of partial deficiency of protoporphyrinogen oxidase enzyme (*PPOX*) in the 7th step of the heme pathway.[2]

Global occurrence of VP is observed mostly heterozygous for genetic defects in the *PPOX* gene which usually exhibit about 50% reduction in *PPOX* enzyme activity.[3] In this case, the genetic analysis showed heterozygote point mutations on c.615A>G, chromosome 1:161138365 corroborating the assumption of VP.

VP can manifest itself as rather common unspecific symptoms. Attacks are usually characterized by abdominal pain, vomiting, constipation and back pain. Psychiatric disturbances such as seizures and anxiety may accompany these symptoms.[4] In adults; blistering, painful cutaneous eschars are found commonly on the sun-exposed skin owing to the accumulation of porphyrin precursors, aminolevulinic acid and porphobilinogen.[3]

Correspondence: Gülbüz SEZGİN
Division of Internal Medicine, Maltepe University Faculty of Medicine, İstanbul, Türkiye
E-mail: gulbuzsezgin@maltepe.edu.tr

Peer review under responsibility of Turkiye Klinikleri Journal of Internal Medicine.

Received: 03 Jul 2022 ***Received in revised form:*** 23 Sep 2022 ***Accepted:*** 23 Sep 2022 ***Available online:*** 28 Sep 2022

CASE REPORT

A 65-year-old female patient came in with bullous lesions on hands (Figure 1, Figure 2), lethargy, increased facial hair and darkened skin. She described the bullous lesions (Figure 3, Figure 4) appearing in August 2019, two centimeters on the metacarpophalangeal and interdigital areas and her left fifth fingernail detached (Figure 5).

Patient's prior medical operations included a thyroidectomy operation in 1976, an ileus operation as a complication of hemorrhoid surgery in 1995, and a total abdominal hysterectomy+bilateral salpingo-oophorectomy in 1997.

She was diagnosed with cutaneous perianal, genital Crohn disease which has been treated with cortisol. She had cranial meningioma operation in 2005, subsequently after the surgery idiopathic seizures have arisen. She was prescribed with phenytoin sodium which had been discontinued after six years

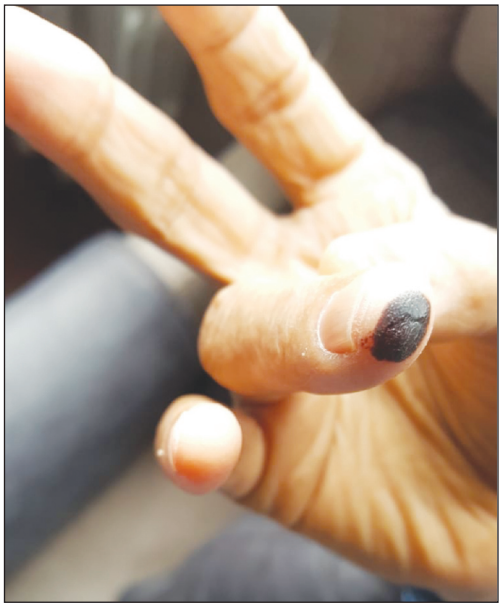

FIGURE 1: Scar tissue of the bullous lesions.

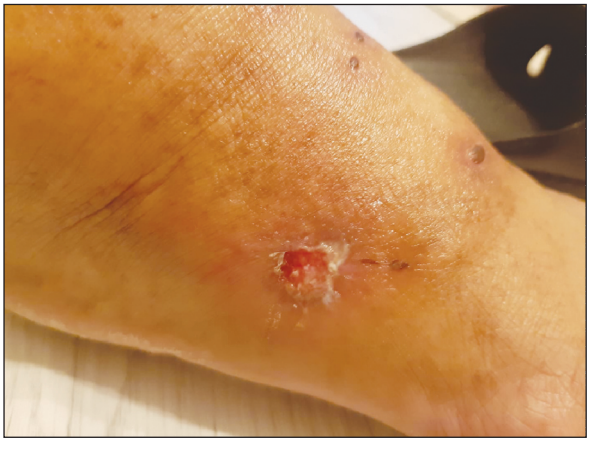

FIGURE 2: Lesions on hand after sun exposure.

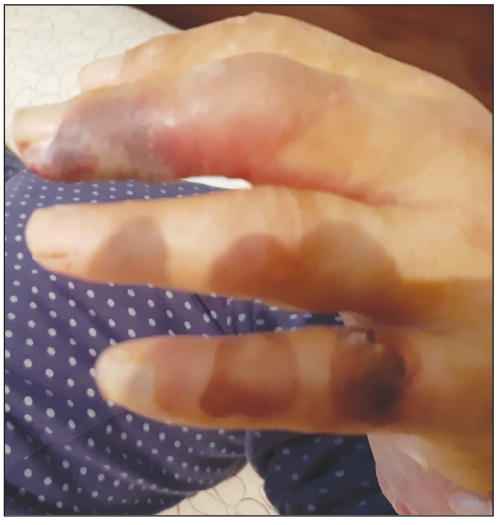

FIGURE 3: Fingernail detached and lesions on fingers.

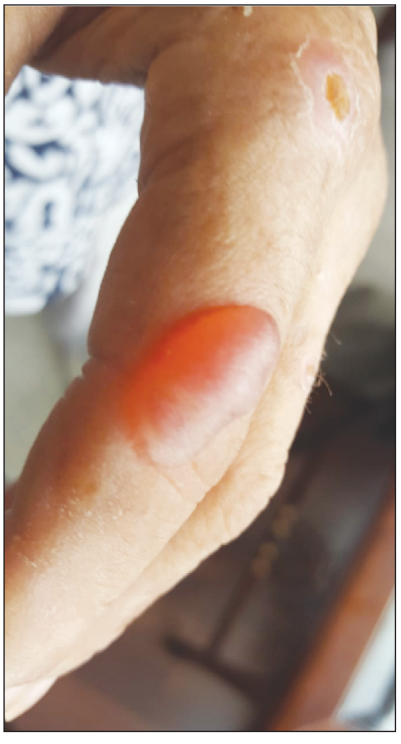

FIGURE 4: Bullous lesion on finger.

FIGURE 5: Fingernail detached and lesions on fingers.

due to the deterioration of renal function also reiterated with high creatinine and phosphorus levels in her lab results (Table 1). Ultimately, chronic renal failure diagnosis was made in 2010. Occasionally she was hospitalized for ascites and abdominocentesis was performed for relief.

She got a positive urine porphobilinogen in 2017, making Porphyria Cutanea Tarda as the primary diagnosis. However, with the genetic test results, the diagnosis was changed to VP. Ehrlich indicator test for porphobilinogen was positive in 2019. She complained about her skin lesions being present at younger ages before her diagnosis. She has been receiving dialysis three times a week since 2019.

Patient had a syncope history in the summer of 2018 after sun exposure; she describes episodes of diplopia, muscle and jaw cramps and syncope since then.

At the beginning of 2022, a lesion in her upper lip was suspected to be malign. Upon surgical removal, she was diagnosed with in situ verrucous carcinoma. Slow waves and paroxysmal activity were seen in the temporoparietal lobe during electroencephalography in 2022 which was performed due to convulsions.

Furthermore, in her family history, her mother suffered from stomach ache episodes, senile osteoporosis, cholecystectomy and chronic liver failure.

Patient is partially cooperative and suffering from convulsions, headaches, dizziness, hair loss, nocturnal dyspnea, anuria, skin lesions especially due to sun exposure (Figure 2, Figure 3, Figure 4), vision problems, mouth lesions, partial hearing loss, diarrhea and constipation, and nausea accompanied with vomiting occasionally.

Her routine medications include pantoprazole, carvedilol, sevelamer hydrochloride, acetylsalicylic acid, allopurinol, levothyroxine sodium, losartan

TABLE 1: Laboratory results of our patient consistent with decreased renal and liver function.

	Patient lab result	Reference values	Comparison
Creatinine	2.9 mg/dL	0.60-1.10 mg/dL (for women)	High
PTH	127 pg/mL	12-65 pg/mL	High
Serum Ca	10.2 mg/dL	8.8-10.2 mg/dL	Normal
Serum P	4.8 mg/dL	2.5-4.5 mg/dL	High
ALP	134 IU/L	53-128 U/L (for women)	High
Ferritin	371 mcg/L	14.5-290 ng/mL (for women)	High
Serum Fe	40.5 mcg/dL	50-170 µg/dL (for women)	Low
TIBC	208 mcg/dL	112-146 µg/dL	High
GGT	73 IU/L	<38 U/L (for women)	High
ALT	36.6 IU/L	<34 U/L (for women)	High
AST	40 IU/L	<31 U/L (for women)	High
Total cholesterol	311 mg/dL	<200 mg/dL	High
Serum albumin	4.1 g/dL	3.5-5.2 g/dL	Normal

kaynak: https://shgmkalitedb.saglik.gov.tr/Eklenti/2635/0/laboratuvartestleripdf.pdf; PTH: Parathyroid hormone; ALP: Alkaline phosphatase; TIBC: Total iron binding capacity; GGT: Gamma-glutamyltransferase; ALT: Alanine transaminase; AST: Aspartate transaminase.

potassium and 10% dextrose infusion for acute porphyria attacks.

The patient's consent was received for publishing this case report.

DISCUSSION

Porphyrias are a group of metabolic diseases that are caused by inherited or acquired derangements in the synthesis of heme.[5] VP is an autosomal dominant type of porphyria that occurs due to disturbances in the *PPOX* gene, which result in decreased activity of *PPOX* synthesized in the 7th stage of heme biosynthesis pathway.[6]

Our patient presented with varying elevated creatinine levels after craniotomy and was followed by nephrology department for over 3 years. The treating physician associated this persistent finding united with abdominal pain, cutaneous lesions and constipation as nephropathy secondary to porphyria. Conversely, misdiagnosis is prevalent in porphyria as a result of false-positive lab tests and symptoms. In a reported case, porphyria masqueraded into an unnecessary operation because of high metanephrine levels, suggestive of pheochromocytoma.[7] Porphyrias are universally rare diseases, inducing overlooked diagnosis. Especially during emergency settings presenting with a porphyria attack, porphyria is widely acknowledged and treated as acute abdomen. This misconception may result in unnecessary laparotomies and treatments that might exacerbate the attack.[8] Consistently, our patient was prescribed phenytoin for her iatrogenic seizures which is also known to exacerbate porphyria attacks.

Osteoporosis, osteopenia, and vitamin D deficiency are frequent findings in VP patients. The contribution of sunlight avoidance measures to these results remains to be clarified. We suggest that the monitoring of serum vitamin D levels in porphyria patients should be mandatory, as well as vitamin D and calcium supplementation.[9] The prevalence of osteoporosis and osteopenia is greatly increased in patients with porphyria.

Treatment strategy during porphyria attacks should consist of a thorough evaluation of the patient's current medications and any porphyrinogenic drugs should been discontinued; glucose loading, hemin, hemarginin or givosiran administration, analgesia and supportive care should be done. Glucose loading should follow as 10% dextrose infusion up to 3-4 L/d and can be sufficient in treatment of mild attacks. However occasionally, intravenous (IV) hemin administration is indicated to control pain and limit neurologic and cardiac progression in acute exacerbation of VP. Hemin administration should be at the discretion of a specialist and should range from 3 to 4 mg/kg doses daily for 3 to 14 days. Sterile water and large peripheral or central vein must be used for injection to eliminate the risk of phlebitis after IV hemin administration. Additionally, for our patient, the dosage of IV hemin administration must be carefully planned with the risk of reversible renal shutdown with doses >2.2 mg/kg as a rare adverse effect in mind. Due to our patient's chronic kidney failure, hemin and hemarginin were avoided in the treatment to prevent further and permenant damage to kidneys.[10] Givosiran, a 5'-aminolevulinate synthase 1-directed small interfering RNA, is another treatment of choice for acute attacks of VP.[11] Some patients with preexisting renal disease suffered from reduced renal function that stabilized with ongoing administration of givosiran.[12]

Moreover, porphyria patients with cutaneous lesions are more prone to skin malignancies such as squamous and basal cell carcinomas. Our patient had a suspicious mass in her lower lip and a subsequent biopsy with clear margins has revealed in-situ verrucous carcinoma, a rare subtype of squamous cell carcinoma constituting 2% of the cases.[13]

It is critical to further educate healthcare professionals in order to comply with the primum non nocere principle.

Our case is unique in the way that porphyrin precursors were accumulated both in the liver and kidney. Due to delayed diagnosis, chronic kidney failure was observed less than 5 years after the initial high creatinine levels making our patient dialysis-dependent. This is a clear reminder that porphyria should be kept in mind in the differential diagnosis in order to avoid attacks bringing long-term complications.

Acknowledgement

We would like to thank Associate Prof. Asuman CÖMERT ERKILINÇ for their contribution in treating our patient.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülbüz Sezgin;* ***Design:*** *Çağdaş Kaya Ayli Heydari;* ***Control/Supervision:*** *Gülbüz Sezgin;* ***Data Collection and/or Processing:*** *Çağdaş Kaya Ayli Heydari;* ***Analysis and/or Interpretation:*** *Gülbüz Sezgin;* ***Literature Review:*** *İlayda Altun, Sude Çavdaroğlu;* ***Writing the Article:*** *Çağdaş Kaya, Ayli Heydari, İlayda Altun, Sude Çavdaroğlu;* ***Critical Review:*** *Çağdaş Kaya, Ayli Heydari, İlayda Altun, Sude Çavdaroğlu;* ***References and Fundings:*** *Çağdaş Kaya, Ayli Heydari, İlayda Altun, Sude Çavdaroğlu;* ***Materials:*** *Çağdaş Kaya, Ayli Heydari, İlayda Altun, Sude Çavdaroğlu.*

REFERENCES

1. Stölzel U, Doss MO, Schuppan D. Clinical guide and update on porphyrias. Gastroenterology. 2019;157(2):365-81.e4. [Crossref] [PubMed]
2. Luvai A, Mbagaya W, Narayanan D, Degg T, Toogood G, Wyatt JI, et al. Hepatocellular carcinoma in variegate porphyria: a case report and literature review. Ann Clin Biochem. 2015;52(Pt 3):407-12. [Crossref] [PubMed]
3. Di Pierro E, Ventura P, Brancaleoni V, Moriondo V, Marchini S, Tavazzi D, et al. Clinical, biochemical and genetic characteristics of Variegate Porphyria in Italy. Cell Mol Biol (Noisy-le-grand). 2009;55(2):79-88. [PubMed]
4. Singal AK, Anderson KE. Variegate Porphyria. 2013 Feb 14 [updated 2019 Dec 12]. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al; editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. [PubMed]
5. Desnick RJ, Balwani M. The Porphyrias: Introduction. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw-Hill; 2018. p.7275.
6. Romaguera D, Puigros MA, Palacin C, Pons A, Tur JA. Nutritional assessment of patients affected by porphyria variegata. Ann Nutr Metab. 2006;50(5):442-9. [Crossref] [PubMed]
7. Stewart MF, Croft J, Reed P, New JP. Acute intermittent porphyria and phaeochromocytoma: shared features. J Clin Pathol. 2007;60(8):935-6. [Crossref] [PubMed] [PMC]
8. Liu YP, Lien WC, Fang CC, Lai TI, Chen WJ, Wang HP. ED presentation of acute porphyria. Am J Emerg Med. 2005;23(2):164-7. [Crossref] [PubMed]
9. Allo G, del Carmen Garrido-Astray M, Méndez M, De Salamanca RE, Martínez G, Hawkins F. Bone mineral density and vitamin D levels in erythropoietic protoporphyria. Endocrine. 2013;44(3):803-7. Erratum in: Endocrine. 2013;44(3):808. Méndez, Manuel [added]. [Crossref] [PubMed]
10. Jones SR, Bell A, Brink G. Treatment of acute intermittent porphyria in the emergency department. J Emerg Nurs. 2014;40(3):257-9; quiz 292-3. [Crossref] [PubMed]
11. Desnick RJ, Balwani M, Anderson KE. Inherited porphyrias. In: Pyeritz R, Korf B, Grody W, eds. Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics. 7th ed. London, U.K: Academic Press; 2021. p.373-411. [Crossref]
12. Gomá-Garcés E, Pérez-Gómez MV, Ortíz A. Givosiran for acute intermittent porphyria. N Engl J Med. 2020;383(20):1989. [Crossref] [PubMed]
13. Rekha KP, Angadi PV. Verrucous carcinoma of the oral cavity: a clinicopathologic appraisal of 133 cases in Indians. Oral Maxillofac Surg. 2010;14(4):211-8. [Crossref] [PubMed]