



CASE REPORT

# Case Report: “Incognito” proteus syndrome [version 1; peer review: 2 approved]

Michelangelo Vestita <sup>1,2</sup>, Angela Filoni<sup>2</sup>, Nicola Arpaia<sup>3</sup>, Grazia Ettore<sup>2</sup>, Domenico Bonamonte<sup>2</sup>

<sup>1</sup>Section of Plastic and Reconstructive Surgery, Department of Emergency and Organ Transplantation, University of Bari, Bari, 70124, Italy

<sup>2</sup>Section of Dermatology, Department of Biomedical Sciences and Clinical Oncology, University of Bari, Bari, 70124, Italy

<sup>3</sup>Section of Dermatology, Miulli Regional Hospital, Bari, 70021, Italy

**V1** First published: 26 Feb 2018, 7:228 (<https://doi.org/10.12688/f1000research.13993.1>)  
 Latest published: 26 Feb 2018, 7:228 (<https://doi.org/10.12688/f1000research.13993.1>)

**Abstract**

Proteus syndrome (PS) is a postnatal mosaic overgrowth disorder, progressive and disfiguring. It is clinically diagnosed according to the criteria reported by Biesecker *et al.*

We describe the case of a 49-year-old woman who presented with a 10-year history of pauci-symptomatic infiltrating plaque lesions on the sole and lateral margin of the left foot, which had been diagnosed as a keloid.

The patient had a positive history for advanced melanoma and a series of subtle clinical signs, such as asymmetric face, scoliosis, multiple lipomas on the trunk, linear verrucous epidermal nevi, and hyperpigmented macules with a mosaic distribution. Even if the clinical presentation was elusive, she had enough criteria to be diagnosed with PS.

This case describes the first evidence, to the best of our knowledge, of pauci-symptomatic PS in adulthood, reports its rare association with advanced melanoma, and illustrates the importance of even minor cutaneous clinical signs, especially when atypical, in formulating the diagnosis of a complex cutaneous condition such as this.

**Keywords**

proteus syndrome, cerebriform, keloid, diagnosis, elusive, hidden

**Open Peer Review**

Reviewer Status

	Invited Reviewers	
	1	2
<b>version 1</b> published 26 Feb 2018	 report	 report

- 1 **Marco Marcasciano**, Sapienza University of Rome, Rome, Italy
- 2 **Giuseppe Micali**, University of Catania, Catania, Italy

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Michelangelo Vestita ([michelangelovestita@gmail.com](mailto:michelangelovestita@gmail.com))

**Author roles:** **Vestita M:** Data Curation, Investigation, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Filoni A:** Investigation, Methodology, Resources, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Arpaia N:** Conceptualization, Formal Analysis, Investigation, Project Administration, Supervision, Validation; **Ettore G:** Data Curation, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Bonamonte D:** Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

**Copyright:** © 2018 Vestita M *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Vestita M, Filoni A, Arpaia N *et al.* **Case Report: “Incognito” proteus syndrome [version 1; peer review: 2 approved]** F1000Research 2018, 7:228 (<https://doi.org/10.12688/f1000research.13993.1>)

**First published:** 26 Feb 2018, 7:228 (<https://doi.org/10.12688/f1000research.13993.1>)

## Introduction

Proteus syndrome (PS) is a postnatal mosaic overgrowth disorder, which was originally described by Cohen and Hayden in 1979<sup>1</sup>. In 1983, the syndrome was named after a minor Greek deity who had the power to change his appearance<sup>2</sup>. The occurrence of this disorder is sporadic, with a prevalence of less than one per million<sup>3</sup>. PS is a progressive, disfiguring disorder caused by a somatic point mutation in *AKT1* leading to gene activation. The product of this gene is involved in cell proliferation and apoptosis suppression, acting through the mammalian target of rapamycin signaling pathway, which may explain the overgrowths in this syndrome<sup>4</sup>. Clinically, this disorder is characterized by typically asymmetric, disproportionate, postnatal overgrowth of tissues derived from any of the three germ layers. While skin, bone, connective, and adipose tissues are most commonly involved, some patients present with overgrowths of the central nervous system, spleen, thymus, or colon. In addition, patients may also present with a range of tumors, pulmonary complications, and a striking predisposition to deep vein thrombosis and pulmonary embolism<sup>5</sup>. PS is clinically diagnosed according to the criteria described by Biesecker *et al.*<sup>6</sup> (Table 1).

## Case

A 49-year-old woman presented with a 10-year history of pauci-symptomatic infiltrating plaque lesions on the sole and lateral margin of the left foot (Figure 1 and Figure 2). The lesions simulated and had been misdiagnosed as keloids, but there was no history of trauma to the area. The patient reported that similar lesions had affected her great-grandmother. The patient had a positive history for stage IV melanoma, and she had finished chemotherapy<sup>7</sup> just 3 months before our observation. Physical examination also revealed multiple lipomas on the trunk, linear verrucous epidermal nevi, and hyperpigmented macules

with a mosaic distribution. Additionally, she presented with an asymmetric face, dysmorphic skull with frontal-parietal hyperostosis, dropped shoulders, scoliosis, and a stiff spine. Her legs were asymmetric with disproportionate overgrowth, the left leg being longer than the right one and having ectatic veins. In addition, computed tomography documented uterine fibromas, and abdominal magnetic resonance imaging demonstrated hepatic angiomas. A skin biopsy specimen from the left foot stained with hematoxylin and eosin revealed remarkable hyperkeratosis, epidermal hyperplasia, dermoepidermal fibrosis with extensive sclerosis of the reticular dermis, thickened collagen bundles, and fat-cell entrapment (Figure 3). We made the diagnosis of Proteus syndrome. No therapeutic intervention was carried out.



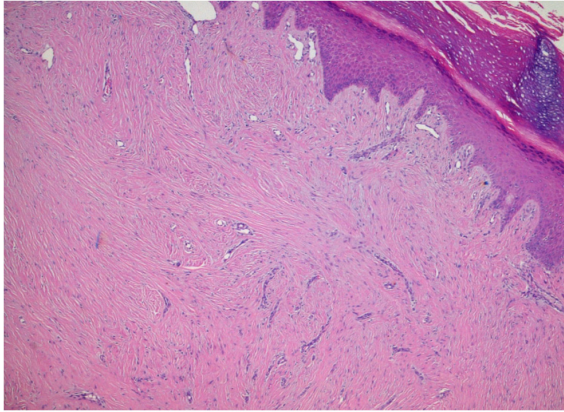
**Figure 1.** Proteus syndrome: Modestly developed connective tissue nevus of the left foot, previously misdiagnosed as a keloid.



**Figure 2.** Proteus syndrome: Lateral view of the affected foot.

**Table 1.** Diagnostic criteria for Proteus syndrome<sup>6</sup>.

<b>General criteria</b>	<ul style="list-style-type: none"> <li>▪ Mosaic lesions</li> <li>▪ Sporadic disease</li> <li>▪ Progressive disease</li> </ul>
<b>Category A</b>	<ul style="list-style-type: none"> <li>▪ Cerebriform connective tissue nevus</li> </ul>
<b>Category B</b>	<ul style="list-style-type: none"> <li>▪ Epidermal nevus (linear verrucous epidermal nevus)</li> <li>▪ Overgrowth of various body tissues</li> <li>▪ Tumors (bilateral ovarian cystadenomas or parotid monomorphic adenomas)</li> </ul>
<b>Category C</b>	<ul style="list-style-type: none"> <li>▪ Dysregulated adipose tissue (lipomas and regional lipo-hypoplasia)</li> <li>▪ Vascular malformations (capillary malformations, venous malformations, and/or lymphatic malformations)</li> <li>▪ Characteristic facial phenotype (long face, minor downward slanting palpebral fissures, low nasal bridge, wide nares, and open mouth at rest).</li> </ul>



**Figure 3. Proteus syndrome: Biopsy from the cerebriform nevus of the foot.** Hematoxylin and eosin (magnification x100).

## Discussion

To meet the diagnostic criteria for PS, a patient must fulfill all three general criteria, plus a single criterion from category A or two criteria from category B or all three criteria from category C (Table 1). Even though our patient had not previously sought medical care, when she presented to us her condition fulfilled the criteria, and the diagnosis of PS was confirmed.

This case illustrates the importance of even minor cutaneous clinical signs, especially when atypical. They should not be overlooked because, together with other clinical and diagnostic findings, they may lead to the diagnosis of a specific condition. This is especially true in mosaic diseases, such as PS, in which

the wide variety of tissue types and cells that are involved may not be apparent at the first examination. Subtle cutaneous forms of PS have been described in infants<sup>4</sup>, but to the best of our knowledge, this is the first case in which the cutaneous signs remained elusive in adulthood. We do not know whether the chemotherapy she had been administered had somehow altered the lesion morphology<sup>7</sup>, but that seems unlikely, as that occurred in adulthood and the patient referred no significant changes in shape and volume.

Correct recognition of pauci-symptomatic “incognito” PS is essential, as PS patients are known to be exposed to a higher risk to develop tumors<sup>1-4</sup>, such as meningiomas, breast and ovarian cancer, parotid adenoma, and others. We do not know whether melanoma occurrence is facilitated by PS, and the literature provides scarce data on this. The association between PS and melanoma in this case is either a novel finding or an incidental coexistence. At present our patient reached the 24 months follow up with no clinical or instrumental signs of recurrence.

## Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

## Competing interests

No competing interests were disclosed.

## Grant information

The author(s) declared that no grants were involved in supporting this work.

## References

- Cohen MM Jr, Hayden PW: **A newly recognized hamartomatous syndrome.** *Birth Defects.* 1979; **15**(5B): 291–296.  
[PubMed Abstract](#)
- Nguyen D, Turner JT, Olsen C, *et al.*: **Cutaneous manifestations of Proteus syndrome. Correlations with general clinical severity.** *Arch Dermatol.* 2004; **140**(8): 947–953.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Doucet ME, Bloomhardt HM, Moroz K, *et al.*: **Lack of mutation-histopathology correlation in a patient with Proteus syndrome.** *Am J Med Genet A.* 2016; **170**(6): 1422–1432.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rodenbeck DL, Greyling LA, Anderson JH, *et al.*: **Early Recognition of Proteus Syndrome.** *Pediatr Dermatol.* 2016; **33**(5): e306–310.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Biesecker LG, Sapp JC: **Proteus Syndrome.** 2012.
- Biesecker LG, Happle R, Mulliken JB, *et al.*: **Proteus Syndrome: diagnostic criteria, differential diagnosis and patient evaluation.** *Am J Med Genet.* 1999; **84**(5): 389–395.  
[PubMed Abstract](#)
- Guida M, Cramarossa A, Fistola E, *et al.*: **High activity of sequential low dose chemo-modulating Temozolomide in combination with Fotemustine in metastatic melanoma. A feasibility study.** *J Transl Med.* 2010; **8**: 115.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

# Open Peer Review

Current Peer Review Status:  

---

## Version 1

Reviewer Report 08 March 2018

<https://doi.org/10.5256/f1000research.15209.r31219>

© 2018 Micali G. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



### Giuseppe Micali

Dermatology Clinic, University of Catania, Catania, Italy

It is an interesting and well-presented case report of pauci-symptomatic, previously overlooked Proteus syndrome in a 49-year-old woman. Proteus syndrome is a rare, complex disorder with multisystem involvement and remarkable clinical variability. The authors highlight the relevance of the recognition of minor cutaneous clinical signs for the diagnosis of minimal forms of the disease, as several complications, some of which life-threatening, may potentially occur in these patients.

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**

Yes

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 28 February 2018

<https://doi.org/10.5256/f1000research.15209.r31217>

© 2018 Marcasciano M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Marco Marcasciano**

Unit of Plastic, Reconstructive and Aesthetic Surgery, Sapienza University of Rome, Rome, Italy

Proteus syndrome is a complex multi-organ mosaic disorder, characterized by progressive overgrowth and disfiguring. The authors did a nice job in describing the occurrence of such a multi-faceted condition in its (rare) minimal symptomatic presentation. To suspect and correctly diagnose a Proteus in view of (apparently) so few clues is indeed challenging. Since the repercussions are relevant (increased incidence of malignancies) the educational message conveyed here is an important one: never underestimate the importance and significance of a given set of signs and symptoms, as subtle as they may be.

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**

Yes

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reader Comment 13 Jan 2019

**Leslie Biesecker**, National Human Genome Research Institute, USA, USA

It is always helpful to see interesting clinical reports. A few things that are puzzling about this report is that the patient does not appear to meet the clinical criteria for this condition. It should be noted that the authors cited our 1999 criteria from AJMG, although those were superseded by the criteria published in 2006 (PMID 16883308). Irrespective of that suboptimal citation, the patient probably meets the general criteria but does not meet specific criterion A because while she probably has a connective tissue nevus, it is not a cerebriform connective tissue nevus (see photos in PMID16883308 for examples that do have this attribute), she does not have two criteria from specific category B nor does she have three criteria from category C. Therefore, I would conclude that clinically, this patient has a segmental (or mosaic) overgrowth disorder and not necessarily

Proteus syndrome.

The second puzzling aspect of this report is that the molecular etiology of Proteus syndrome was elucidated eight years ago (PMID 21793738), yet this test was not performed on this patient. While there can be valid reasons for not performing such testing in a clinical context, to claim a patient has a diagnosis in a scientific publication without confirming that diagnosis molecularly is problematic. Should the authors be unable to access clinical testing for this patient, we would be willing to provide that free of charge should this lady be willing to enroll in our research study.

As we have documented, diagnostic confusion between Proteus syndrome and related overgrowth disorders is a common problem (PMID 15372514). PIK3CA-related overgrowth spectrum (PMID 25557259) is probably 100X more common than is Proteus syndrome, and inexperienced clinicians frequently confuse these entities.

Finally, these authors claim that "This case describes the first evidence, to the best of our knowledge, of pauci-symptomatic PS in adulthood..." I would suggest that the authors review PMID 24850616 for a prior example of just that.

Again, the authors are to be congratulated for identifying this interesting patient, though the lessons learned may be quite distinct from that which they assert.

**Competing Interests:** No competing interests were disclosed.

---

## Comments on this article

### Version 1

Reader Comment 09 Apr 2019

**Leslie Biesecker**, MGMGB/NHGRI/NIH, Bethesda, USA

This is a very interesting, though somewhat atypical patient. It is always important in published scientific work to meet the highest standards of rigor. It is worth noting that we have a paper in press showing that the cerebriiform connective tissue nevus can be observed rarely in patients with PIK3CA-related overgrowth spectrum. As the mutation test for Proteus syndrome is readily available, this should be done to confirm the validity of this report. We would be pleased to do this free of charge, in the interests of scientific rigor. Please do contact us to arrange this.

**Competing Interests:** We study Proteus syndrome.

---



The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**