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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Transgrediens pachyonychia congenita (PC): case series of a nonclassical PC presentation

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Accepted for publication
18 July 2011

Funding sources
This study was supported by funding (to S.A.L.) from the Pachyonychia Congenita Project (Salt Lake City, UT, U.S.A.; http://www.pachyonychia.org), sponsor of the International Pachyonychia Congenita Research Registry (IPCRR) and characterized via telephone survey and photography.

Results
Seven patients with PC in the IPCRR were confirmed to have transgrediens lesions on the dorsal feet (six KRT6A mutations; one KRT16 mutation). Six cases had pre-existing nontransgrediens keratoderma and all cases reported standing, wearing shoes, foot moisture, and/or infection as exacerbating or predisposing factors. Improvement, reported in six cases, was attributed to use of antibiotics or gentian violet, or improved footwear.

Conclusions
Transgrediens involvement of the dorsal feet is a rare manifestation of mutation-confirmed PC and may be more common in patients who carry a KRT6A mutation. Trauma, friction, infection and wound healing may exacerbate or predispose toward transgrediens lesions. It remains to be proven whether transgrediens-associated infection is causal or represents a primary or secondary process. Patients with PC who develop transgrediens lesions may benefit from fungal and bacterial cultures, followed by appropriate antimicrobial treatments. Efforts to decrease skin friction and moisture may also improve and/or prevent transgrediens spread.

**Summary**

Background
Pachyonychia congenita (PC) is a rare keratin disorder that typically presents with nail dystrophy and focal plantar keratoderma. We present seven cases of PC with transgrediens involvement of the dorsal feet.

Objectives
To document the extension of their disease to the dorsum of the feet in patients with mutation-confirmed PC, to report the natural history of PC with such transgrediens involvement, to generate hypotheses regarding aetiology, and to suggest prevention and treatment modalities.

Methods
Genetically confirmed cases of PC with transgrediens foot involvement were verified through the International Pachyonychia Congenita Research Registry (IPCRR) and characterized via telephone survey and photography.

Results
Seven patients with PC in the IPCRR were confirmed to have transgrediens lesions on the dorsal feet (six KRT6A mutations; one KRT16 mutation). Six cases had pre-existing nontransgrediens keratoderma and all cases reported standing, wearing shoes, foot moisture, and/or infection as exacerbating or predisposing factors. Improvement, reported in six cases, was attributed to use of antibiotics or gentian violet, or improved footwear.

Conclusions
Transgrediens involvement of the dorsal feet is a rare manifestation of mutation-confirmed PC and may be more common in patients who carry a KRT6A mutation. Trauma, friction, infection and wound healing may exacerbate or predispose toward transgrediens lesions. It remains to be proven whether transgrediens-associated infection is causal or represents a primary or secondary process. Patients with PC who develop transgrediens lesions may benefit from fungal and bacterial cultures, followed by appropriate antimicrobial treatments. Efforts to decrease skin friction and moisture may also improve and/or prevent transgrediens spread.

Pachyonychia congenita (PC) is a rare, autosomal, dominant-negative keratin disorder associated with mutations in keratins KRT6A, KRT6B, KRT16 and KRT17.1 Recent data suggest that KRT6A and KRT16 mutations are more common than KRT6B and KRT17 mutations.1 PC manifests most commonly with nail dystrophy and painful focal plantar keratoderma. Additionally, PC can affect the palms, oral mucosa, tongue and teeth. Patients with KRT17 mutations are more likely to have natal teeth and develop steatocystomas while patients with KRT6A mutations more commonly manifest oral leucokeratosis.1–4

Classically, the plantar involvement presents as exquisitely painful, focal keratoderma restricted to pressure points on the plantar surface.2 We present seven cases of PC from the International Pachyonychia Congenita Research Registry (IPCRR) with transgrediens (i.e. extension of lesions beyond the plantar surface) involvement of the dorsal feet, followed by a discussion of possible aetiologies and treatments of this transgrediens variant of PC. It is important for clinicians to be aware that patients with PC may develop lesions of the dorsal feet and that dorsal foot involvement does not rule out the diagnosis of PC. Some cases of dorsal foot involvement in patients with PC can be improved with treatment.

Materials and methods

The International Pachyonychia Congenita Research Registry

The IPCRR is a research registry resource approved by the Western Institutional Review Board (WIRB) and is in compliance with the guidelines of the Western Institutional Review Board. The IPCRR was reviewed and approved by the Western Institutional Review Board of the University of Utah. The IPCRR is a research registry resource approved by the Western Institutional Review Board (WIRB) and is in compliance with the guidelines of the Western Institutional Review Board. The IPCRR was reviewed and approved by the Western Institutional Review Board of the University of Utah.
with all the principles of the Helsinki Accord (WIRB no. 1057496). Participant recruitment is primarily by self- or family referral to the web-based registry (http://www.pachyonychia.org), although physician referral occurs as well. Participants in the registry have the option to complete an epidemiological, genetic and medical history questionnaire, provide clinical photographs, and receive genetic counselling and mutation testing (KRT6A, KRT6B, KRT16, KRT17). Each participant who completes a questionnaire and provides a series of standard photographs (or receives a physical examination by an IPCRR physician) undergoes a medical consultation in order to establish the clinical diagnosis and determine the appropriateness of genetic testing. Mutation status is determined by sequence analysis in a research laboratory (F.J.D.S.; Dundee, Scotland, U.K.) and is verified in the clinical laboratory of GeneDx (Gaithersburg, MD, U.S.A.; CLIA no. 21D0969951).

Selection of patients

Seven patients with PC in the IPCRR were identified with a history of dorsal foot lesions. Identification was based on self-report via the standard intake questionnaire, physician consultation, or physical examination and/or update-reporting to IPCRR staff of dorsal foot lesions.

Data collection

Patients or their legal guardian (in the case of patient 5, who is a minor) were contacted via telephone and informed that the IPCRR was conducting a telephone survey of patients with PC with dorsal foot lesions, with planned publication of the survey results. Six of the seven phone interviews were conducted in English. The interview of patient 1 was conducted via an interpreter in his native language, Spanish. The interviewed parent of patient 5 is a native Dutch speaker but was fluent and comfortable conducting the interview in English. All other patients are native English speakers. After verbal agreement to participate in the survey, patients/guardians were interviewed in a systematic manner, utilizing a list of questions developed by the authors of this paper. The questions covered information regarding age of onset of PC plantar lesions, age of onset and duration of dorsal foot lesions, exacerbating and mitigating factors related to dorsal foot involvement, and treatment responses (see Supporting Information). All patients/guardians who were contacted agreed to participate. Patients were encouraged to send recent photos of their feet to the IPCRR at the conclusion of the telephone survey. Information from previous communications with the IPCRR, including the initial IPCRR registration questionnaire, physician intake form, photographs and results of keratin mutation testing were reviewed for each patient.

Results

Pachyonychia congenita is an ultrarare disorder and the seven patients described below live in diverse regions of the world, have variable medical care, and medical records from their local care providers were variably available through the IPCRR. Therefore, the clinical features, diagnoses and responses to therapy described below are based primarily upon patient reports and available photographs (Table 1, Fig. 1).

Patient 1

Patient 1 is a 27-year-old Hispanic male KRT6A mutation carrier. Plantar keratoderma developed at age 4 years, and painful

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Mutation</th>
<th>Age of plantar keratoderma onset (years)</th>
<th>Age of transgrediens involvement onset (years)</th>
<th>Exacerbating factors</th>
<th>Treatments associated with improvement in transgrediens involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Male</td>
<td>K6a p.Asn171Tyr</td>
<td>4</td>
<td>19</td>
<td>Standing wearing shoes, foot moisture, infection</td>
<td>Antibiotics, antifungals</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>Female</td>
<td>K6a p.Phe174Ser</td>
<td>4</td>
<td>12</td>
<td>Standing wearing shoes</td>
<td>Foam rubber shoe insert</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>Male</td>
<td>K6a p.Asn172del</td>
<td>5</td>
<td>5</td>
<td>Standing wearing shoes, infection</td>
<td>Topical mupirocin, ciclopirox, sodium sulfacetamide, chlorhexidine washes</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>Female</td>
<td>K6a p.Glu472Lys</td>
<td>1</td>
<td>51</td>
<td>Infection</td>
<td>Antifungals</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>Female</td>
<td>K16 p.Arg127Pro</td>
<td>1</td>
<td>4</td>
<td>Standing wearing shoes, infection</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>Male</td>
<td>K6a p.Asn172del</td>
<td>Toddler</td>
<td>10</td>
<td>Standing wearing shoes, foot moisture, infection</td>
<td>Antibiotics, elastic compression wraps, gentian violet</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>Female</td>
<td>K6a p.Asn172del</td>
<td>Young child</td>
<td>55</td>
<td>Standing wearing shoes, foot moisture, infection</td>
<td>Gentian violet, gentamicin ointment</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of patients with pachyonychia congenita with transgrediens foot lesions: exacerbating factors and treatments associated with improvement

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redness, scaling and weeping on his bilateral dorsal toes and feet began at age 19 years (Fig. 1a). He reported that the dorsal foot involvement is nearly constantly present but worsens when he spends increasing time on his feet wearing shoes, with increased perspiration of his feet, and with infection. Treatment with antibiotics and antifungals has improved but not resolved his transgrediens lesions. The patient was clinically examined at PC patient support meetings in August 2005 and June 2007 by authors S.A.L. and P.R.H. and found to have webspace and dorsal foot involvement. A webspace culture in 2007 resulted in heavy growth of *Citrobacter koseri* and *Enterobacter aerogenes*. The patient was treated with oral ciprofloxacin and experienced an improvement of his transgrediens lesions. He is the only member of his family with PC.

**Patient 2**

Patient 2, a KRT6A mutation carrier, is a 35-year-old white woman who reported that she first developed plantar keratoderma at age 4 years and developed tender redness and scaling of her dorsal feet at approximately 12 years of age. This lasted 13 years until she quit wearing boots and began wearing slip-on sneakers, cotton socks and hand-made high-density foam rubber inserts cut to cradle her feet. With continued use of the foam rubber inserts, she reports that she has remained free of lesions on her dorsal feet and has been able to increase her mobility and time standing. She does not have family members with PC.

**Patient 3**

This 64-year-old man is a KRT6A mutation carrier and he developed plantar keratoderma and scale, redness and pain of the dorsal feet at 5 years of age. The dorsal foot involvement flared with increased time on his feet, increased time wearing shoes, and infection. Four years ago, he began a daily prophylactic antimicrobial regimen of topical mupirocin, ciclopirox and sodium sulfacetamide to his feet and twice-weekly whole body chlorhexidine washes. Since starting the antimicrobial regimen, he reports his dorsal, but not plantar feet have been free of lesions. Other members of his family with PC do not have transgrediens involvement.

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Fig 1. Transgrediens foot lesions in patients with pachyonychia congenita. (a) Patient 1; (b) patient 6 before use of topical gentian violet; (c) patient 6 after near daily use of topical gentian violet; (d) patient 7 before use of topical antimicrobials; (e) patient 7 after use of daily antimicrobials.
Patient 4

This is a 53-year-old female KRT6A mutation carrier who developed plantar keratoderma at age 1 year. At 51 years of age, she developed transgrediens involvement with blistering, erythema and purulent discharge of the right dorsal foot. She was hospitalized and treated with multiple oral and intravenous antibiotics for broad-spectrum bacterial coverage. She was also treated with wound debridement. Since the episode of transgrediens involvement she treats her feet with daily salicylic acid and antimicrobial chloroxylenol topical applications. The patient’s father, sister and two daughters also have PC, but none has had dorsal foot involvement.

Patient 5

Patient 5 is a 14-year-old female KRT16 mutation carrier with plantar keratoderma since age 1 year, who began having painful, scaling, erythematous, weeping plaques of the dorsal aspect of her feet at 4 years of age. Her transgrediens lesions seemed to be precipitated by spending increased time on her feet and in shoes. Examinations of her feet at PC patient support meetings in July 2006 and July 2008 by author S.A.L. revealed transgrediens PC-appearing keratoderma, as well as interdigital maceration. The dorsal foot involvement continues to wax and wane, associated with time spent on her feet. No other members of her family have PC.

Patient 6

Patient 6, a KRT6A mutation carrier, is a 63-year-old man who developed plantar keratoderma as a toddler, followed by dorsal foot involvement at age 10 years, both of which persist today. He describes dorsal foot redness and scaling that waxes and wanes, worsening with foot moisture and infections (see Fig. 1b for clinical appearance). Generally, his dorsal involvement starts as blisters on the dorsal toes and spreads across the dorsal foot. Dorsal involvement improves with topical and oral antibiotic treatments, as well as wrapping his feet in elastic compression bandages to avoid contact with his shoes and decrease swelling. He reports substantial improvement in his dorsal foot involvement since starting application of 2% gentian violet solution (daily to every other day; see Fig. 1c for post-gentian violet change). The patient was examined by author S.A.L. at PC patient support meetings in March and September of 2009 before the patient began using gentian violet solution. He does not have any family members with PC.

Patient 7

This 66-year-old female KRT6A mutation carrier reports developing painful plantar keratoderma as a young child and delayed dorsal foot involvement with erythema, scale and weepiness at age 55 (Fig. 1d). Spending more time on her feet wearing shoes, foot moisture and infection exacerbate the dorsal foot lesions. She reports that she has been diagnosed with repeated bacterial infections of her dorsal feet and toes over the past 10 years and that these improved with antibiotic treatment but quickly relapsed when medication was discontinued. Over 1 year ago she began using topical gentian violet and gentamicin ointment twice daily. Since starting the topical antimicrobial regimen she reports significant improvement and near resolution of the dorsal foot lesions (Fig. 1e) without resolution of the plantar lesions. The patient was examined by authors on three occasions at patient support meetings in June 2007 (S.A.L., P.R.H.), March 2009 (S.A.L.) and September 2009 (S.A.L.); marked improvement was noted after starting the topical antimicrobial regimen. She does have other family members with PC. She believes her aunt may have had transgrediens involvement but she is unsure of this. She reports other family members with PC do not have transgrediens involvement.

Discussion

Although PC classically causes a nontransgrediens focal plantar keratoderma, patients with genetically confirmed PC can develop transgrediens foot lesions as evidenced by this case series. These seven cases highlight that transgrediens lesions can present with varying severity and at least in some cases improve with environmental and/or pharmaceutical interventions. However, this clinical manifestation is relatively rare among patients with PC. Three of the seven patients in this series have other family members with PC, but none of these other family members have definitively exhibited the transgrediens pattern of involvement to date. This suggests that the transgrediens pattern of involvement is not a separate subtype of PC, but rather is a variably expressed phenotype that is probably influenced by environmental factors or co-inherited modifying genes.

A unifying hypothesis with respect to the pathomechanism of transgrediens involvement in PC centres on the role of wound healing in this particular genodermatosis. PC keratin expression is activated by the process of wound healing and is higher in areas exposed to recurrent sheer forces (e.g. plantar surfaces). The factors found to be associated with transgrediens involvement in PC, including increased time standing, increased friction to the skin and infection might stimulate a wound healing response, particularly when the events are prolonged or recurrent. Wound healing would increase the proportion of PC keratins expressed in the skin and could potentially lead to prolonged, increased fragility in this area. With respect to the local microbial environment, it is unclear whether the microorganisms observed in the area are non-pathogenic bystanders or whether an infectious process might initiate the injury. Increased hydration of the stratum corneum (associated with hyperhidrosis) on the dorsal foot surface, may increase sheer stress forces on the skin and result in increased cellular damage and wound healing. Discrimination of the role of infectious vs. noninfectious or inflammatory trauma is complicated by the close association of these clinical...
findings and by the fact that many antimicrobial regimens have anti-inflammatory and antimicrobial effects. Additionally, more careful and rigorous microbial isolation and documentation is needed.

Two of the seven patients reported improvement with the use of gentian violet. Gentian violet has been used topically for many decades and has broad-spectrum bactericidal and fungicidal activities. Interestingly, gentian violet also has anti-inflammatory properties. In the skin, angiopoietin-2 has been identified as a major component of vascular permeability, and angiopoietin-2 has been shown to be proinflammatory as well. Triphenylmethanes, such as gentian violet, are potent inhibitors of nicotinamide adenine dinucleotide phosphate oxidases that have been shown to downregulate angiopoietin-2, and have been clinically efficacious in the treatment of vascular haemangiomas of infancy. The reported benefit of gentian violet in transgrediens PC could be due to the antimicrobial or anti-inflammatory properties of the drug or a combination of these effects.

This series is limited by its data collection method. All data were based on patients’ recall of their disease state and treatments. It was not possible to verify systematically patient reports with objective data. Further, this series cannot quantify the prevalence or incidence of transgrediens lesions in patients with PC at large. Despite these limitations, it is the first report of a particularly troublesome manifestation of the disease and increased awareness will provide valuable assistance to clinicians confronted with this problem.

Many dermatologists will care for only a small number of patients with PC during their entire career. With such little experience of patients with PC, it can be difficult to determine what is a ‘normal’ manifestation of PC and what is a secondary process that may respond to appropriate treatment. This case series highlights that some patients with PC who develop transgrediens foot lesions may benefit from yeast and bacterial cultures, followed by appropriate antimicrobial treatments. While the safety, efficacy and mechanisms of action of gentian violet may vary and patients should be monitored for potential adverse events with long-term use. Efforts to decrease skin friction and moisture are also likely to help improve and/or prevent transgrediens spread of PC.

What's already known about this topic?
- Pachyonychia congenita (PC) is rare disease that classically has nontransgrediens focal plantar keratoderma.
- Limited data exist about nonclassical transgrediens foot disease in patients with known PC.

What does this study add?
- This is the first published case series examining transgrediens foot involvement in PC.
- It discusses prevention and treatment strategies that will assist clinicians in management of patients with PC with transgrediens disease.

Acknowledgments

We gratefully acknowledge the patients and their families who participated in this study. We also acknowledge support from the International Pachyonychia Congenita Research Registry.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article.

**Data S1.** Telephone questionnaire examining transgrediens pachyonychia congenita.

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