in 70% of individuals with the severe generalized form of the disease.[3] Inflammation is a typical feature of invasive sporadic and RDEB-associated cSCC and carcinogenesis is accompanied by increased protein and extracellular cell-surface protease activity resulting in modification of the tumour microenvironment. The main changes include cleavage of the extracellular matrix, activation of growth factors and pro-inflammatory mediators, as well as recruitment of inflammatory cells. Together, these processes potentiate the neoplastic progression leading to local tumour cell invasion, entry into the vasculature and metastasis to distal sites.[4] This is significant as the tumour microenvironment has been implicated as the driving mechanism of cancer development in tissue-damage-driven RDEB-associated cSCC.[5] During the later stages of cSCC progression, tumour cells induce increased expression of complement components and inhibitors, with serine protease commonly overexpressed in different cancers including invasive cSCC.

Previous studies have reported that in addition to complement activation, complement components may play a role in tumour progression in an autocrine manner.[6] In this issue of the *BJD*, Riihila *et al.* report tumour-cell-derived serine proteases, C1r and C1s, known initiators of the classical pathway activation of the complement system, to be novel biomarkers and putative therapeutic targets in cSCC.[1] The authors show that C1r and C1s expression is markedly elevated in invasive sporadic and RDEB-associated cSCC while their knockdown in cSCC cells inhibited activation of the extracellular signal-related kinase (ERK) 1/2 and Akt pathway, promoted cSCC apoptosis, and suppressed growth and vascularization of human cSCC xenograft tumours *in vivo*.[1] Interestingly, RDEB-SCC sections had the strongest C1r and C1s staining, and the knockdown of C1r and C1s upregulated the production of matrix metalloproteinase-9 in cSCC cells.[1] Additionally, previous studies have shown that extracellular C1s can cleave and inactivate alarmin high-mobility group box (HMGB1), hence regulating inflammation and suppressing proinflammatory cytokine production.[7] These findings suggest that tumour-derived serine proteases, C1r and C1s, can be used as molecular markers in assessing cSCC progression while inhibitors of these serine proteases may have therapeutic value. The feasibility of using complement components as biomarkers for assessing disease progression has been demonstrated in cSCC[8] and 'First in RDEB' phase II clinical trials to assess tumour targeting with late-stage, metastatic and/or unresectable SCC, using different kinase inhibitors are currently underway.[5]

'Free' serine proteases can be found in pathological sera or fluid of patients; therefore, it would be interesting to see if this is the case in RDEB-SCC patient sera or blister fluid. Future studies should investigate the relationship or association of these serine proteases with clinicopathological characteristics or patient survival, especially in the RDEB patient population, and investigate therapeutic potential of C1r and C1s serine proteases inhibitors for the treatment of invasive sporadic and RDEB-associated cSCC. In summary, this article helps us to better understand the role of serine proteases in cSCC progression and may lead to novel therapeutic interventions against aggressive cSCC.

Z. Kopecki

Regenerative Medicine Laboratory, Future Industries Institute, University of South Australia, Adelaide, South Australia Australia
E-mail: zlatko.kopecki@unisa.edu.au

References

1 Riihilä P, Viiklepp K, Nissinen L *et al.* Tumour-cell-derived complement components C1r and C1s promote growth of cutaneous squamous cell carcinoma. *Br J Dermatol* 2020; **182**:658–70.
2 Boyle S, Kopecki Z. Mechanical force and actin dynamics during cutaneous squamous cell carcinoma (cSCC) progression: opportunities for new treatment modalities. In: *Squamous Cell Carcinoma – Hallmark and treatment modalities*. London: IntechOpen Limited, (forthcoming); chapter available as open access online at: https://doi.org/10.5772/intechopen.86041
3 Fine JD, Bruckner-Tuderman L, Eady RA *et al.* Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol* 2014; **70**:1103–26.
4 Murray AS, Varela FA, List K. Type II transmembrane serine proteases as potential targets for cancer therapy. *Biol Chem* 2016; **397**:815–26.
5 Atanasova VS, Pourreyron C, Farshchian M *et al.* Identification of rigosertib for the treatment of recessive dystrophic epidermolysis bullosa-associated squamous cell carcinoma. *Clin Cancer Res* 2019; **25**:3384–91.
6 Cho MS, Vasquez HG, Rupaimoole R *et al.* Autocrine effects of tumor-derived complement. *Cell Reports* 2014; **6**:1085–95.
7 Yeo JG, Leong J, Arkachaisri T *et al.* Proteolytic inactivation of nuclear alarmin high-mobility group box 1 by complement protease C1s during apoptosis. *Cell Death Discov* 2016; **2**:16069.
8 Harris CL. Expanding horizons in complement drug discovery: challenges and emerging strategies. *Semin Immunopathol* 2018; **40**:125–40.

Funding sources: Z.K. is supported by a Future Industries Institute Foundation Fellowship from the University of South Australia and research funding from the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) Australia.

Conflicts of interest: none to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Audio S1 Author audio.

Pachyonychia congenita and botulinum toxin

DOI: 10.1111/bjd.18784

Linked Article: Koren *et al.* *Br J Dermatol* 2020; **182**:671–677.

Pachyonychia congenita (PC) is a rare autosomal dominant condition that is mainly characterized by nail dystrophy,

plantar pain and plantar keratoderma. Plantar pain is very common in PC and can be so severe that patients are unable to walk and may require mobility aids/wheelchairs.[1] The pain is thought to be related to skin fragility with blister formation under calluses. This may be exacerbated by hyperhidrosis.[2] Neuropathic pain is present in two-thirds of patients with PC.[3] In this issue of the *BJD*, Koren *et al.* describe their protocol for treating PC plantar keratoderma pain with botulinum toxin type A (Btx).[4]

Btx has been in clinical use for over 15 years in the treatment of muscle spasms, glabellar lines and axillary hyperhidrosis, where its effects are due to the blockade of acetylcholine exocytosis at the neuromuscular junction resulting in muscle paralysis or blocking eccrine gland sweat production. In addition, Btx can reduce inflammatory and neuropathic pain by acting on neurokinin-1 receptor-expressing neurons in the central nervous system or by blocking pain-related neurotransmitters such as substance P, glutamate and even reducing levels of the inflammatory pain-related protein transient receptor potential vanilloid 1 in the peripheral nervous system.[5] Our understanding of these additional mechanisms of action of Btx has led to many off-label disease treatments in dermatology, with some success.[6]

Koren *et al.* have been able to exploit these Btx effects and report results of plantar Btx treatment in five patients with PC-K16 (*KRT16* mutation). Significant improvement was found in all five patients treated, with a 20–72% reduction in a PC-specific quality-of-life questionnaire score. The improvement was most marked in pain-level and walking-distance scores and the magnitude of change seen is likely to be transformative for these patients. Interestingly, the greatest improvement was seen in those who had multiple treatments (confirming previous reports),[7] particularly those whose treatments occurred at least every 100 days. The typical duration of effect of 3–4 months is similar to our unit's experience of primary plantar hyperhidrosis treatment, although we recognize that some dermatology services may find 100-day treatment cycles difficult to implement.

We welcome the detailed description of how to perform the treatment, which includes details of nerve blocks for anaesthesia, the optimal sites for treatment (painful areas and calluses only) and the typical doses of the different subtypes of Btx. We were interested in the use of ultrasound-guided nerve blocks, which appeared to be effective with low pain scores for both the nerve block and the Btx treatment. In our centre, we do not yet treat plantar PC keratoderma with Btx, although we have many years of experience of using Btx in the treatment of primary plantar hyperhidrosis with effective pain relief via physician-administered Entonox® inhalation (50% nitrous oxide and 50% oxygen mixture) (BOC Healthcare, Manchester, U.K.). Others have reported success with the use of ice-cooling combined with topical anaesthetic cream.[7] We believe that finding suitable anaesthesia tailored to site-specific resources will be necessary for widespread implementation of this treatment.

The authors point out that this treatment may not be generalizable to patients with other PC genotypes, but we believe that this may not prove to be an issue as previous reports have shown a good response to Btx in the very painful PC-K6a subtype.[1,7,8] They also point out that this is an uncontrolled study and we would like future studies to determine whether there is true cumulative improvement with multiple treatments rather than repeated treatments being offered only to responders. Understanding this would help to manage expectations in patients with less dramatic initial responses; however, Koren *et al.* have given us a framework for effective treatment of plantar pain in patients with PC and for future research in this area.

Acknowledgments: The authors thank Edel O'Toole (Centre for Cell Biology and Cutaneous Research, The Blizard Institute, Barts and the London School of Medicine and Dentistry, London, U.K.) for her critical review of this commentary.

B.R. Thomas [1,2] and A. Sahota[2]

[1]*Centre for Cell Biology and Cutaneous Research, The Blizard Institute, Barts and the London School of Medicine and Dentistry, 4 Newark Street, London E1 2AT U.K.;* [2]*Department of Dermatology, Barts Health NHS Trust, Whitechapel Road, London E1 1BB U.K.*
E-mail: b.r.thomas@qmul.ac.uk

References

1 Swartling C, Vahlquist A. Treatment of pachyonychia congenita with plantar injections of botulinum toxin. *Br J Dermatol* 2006; **154**:763–5.
2 Goldberg I, Sprecher E, Schwartz ME, Gaitini D. Comparative study of high-resolution multifrequency ultrasound of the plantar skin in patients with various types of hereditary palmoplantar keratoderma. *Dermatology* 2013; **226**:365–70.
3 Brill S, Sprecher E, Smith FJD *et al.* Chronic pain in pachyonychia congenita: evidence for neuropathic origin. *Br J Dermatol* 2018; **179**:154–62.
4 Koren A, Sprecher E, Reider E, Artzi O. A treatment protocol for botulinum toxin injections in the treatment of pachyonychia congenita-associated keratoderma. *Br J Dermatol* 2020; **182**:671–7.
5 Maiaru M, Leese C, Certo M *et al.* Selective neuronal silencing using synthetic botulinum molecules alleviates chronic pain in mice. *Sci Transl Med* 2018; **10**:eaar7384.
6 Grando SA, Zachary CB. The non-neuronal and nonmuscular effects of botulinum toxin: an opportunity for a deadly molecule to treat disease in the skin and beyond. *Br J Dermatol* 2018; **178**:1011–19.
7 Swartling C, Karlqvist M, Hymnelius K *et al.* Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenita. *Br J Dermatol* 2010; **163**:1072–6.
8 Gonzalez-Ramos J, Sendagorta-Cudos E, Gonzalez-Lopez G *et al.* Efficacy of botulinum toxin in pachyonychia congenita type 1: report of two new cases. *Dermatol Ther* 2016; **29**:32–6.

Conflicts of interest: none to declare.