

In other words, we were interested in the frequency and not in the duration of AEs, and therefore we considered the incidence of AEs instantaneous.

As an alternative to using time in the condition of AEs as a time-varying covariate, one could come up with a complex modeling approach, such as defining a continuously time-varying “potential” for AEs and then consider the actual AE incidence to be a Poisson point process realization with intensity defined by this potential function. However, adding this extra layer to the model increases complexity drastically and precludes the opportunity to use standard statistical software for analysis.

The specific approach we implemented to account for the entanglement of AEs with time was to use a multivariate Cox regression model where the “time effect” was accounted for by including the number of pembrolizumab cycles received as an additive predictor. We believe that this is clearly stated in our report. We corrected for the number of cycles rather than time as a continuous variable because some patients received the drug every 2 weeks and some every 3 weeks, and therefore the number of cycles was most important to account for. In our article we discuss that the results have to be interpreted with caution, and we are aware that the analysis performed may not fully mitigate the entanglement of time to progression and the time on treatment. In only 1 group (Figure 3C) did we find significant correlation between the time to progression and the development of AEs when corrected for the number of pembrolizumab cycles.¹

Finally, Hwang et al recommend that the analysis be done by an experienced statistician, and we reply that this analysis was supervised and recommended by experienced statisticians from the University of California, San Francisco. We invite Dr Hwang and colleagues to contact us if they are in need of further explanations.

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Identification of a *CAST* Mutation in a Cohort Previously Misdiagnosed as Having Autosomal Recessive Pachyonychia Congenita

To the Editor This letter corrects our diagnosis from 1986, documents the *CAST* mutation in our patients from that time, and adds to the list of genodermatoses that may mimic pachyonychia congenita (PC).

The gold standard for diagnosis of genetic skin diseases is the demonstration of the causative gene mutation. The dominantly inherited genodermatosis PC is caused by a mutation in *K6a*, *K6b*, *K6c*, *K16*, or *K17*.¹ Pachyonychia congenita can be clinically misdiagnosed, with reports of Clouston syndrome mimicking PC, and the correct diagnosis can only be made by gene mutational analysis.²

In 1986, prior to the establishment of the causative PC keratin gene mutations, we reported PC with autosomal recessive inheritance.³ When one of our original patients was eventually contacted for genetic assessment in 2015 and tested negative for any of the known keratin mutations causing PC, he underwent whole-exome sequencing, which established the correct diagnosis of PLACK syndrome (peeling skin, leukonychia, acral punctate keratoses, cheilitis, and knuckle pads) in our cohort.

PLACK syndrome was recently described by Lin et al⁴ as a new type of autosomal recessive generalized peeling skin syndrome caused by mutations in the *CAST* gene. The authors describe Chinese and Nepalese patients as well as our “autosomal recessive PC” family. By whole-exome sequencing, Lin et al found that all affected individuals had loss-of-function mutations in the *CAST* gene that encodes for the protein calpastatin. The *CAST* mutation in our patients was a homozygous frameshift mutation, c.1750delG, p.Val584Trpfs*37. Different homozygous mutations were identified in the Chinese and Nepalese families. Similar to the other 2 families with PLACK syndrome, our patients had peeling skin, leukonychia, acral punctate keratoses, and angular cheilitis. Our patients differed from the other 2 families with PLACK syndrome in that they had extensive oral leukokeratosis, more diffuse plantar keratoderma, and no knuckle pads. To our knowledge, the only other report of autosomal recessive PC was in 1977, a Malaysian girl whose parents were first cousins.⁵ This case was never supported by a molecular diagnosis.

All genetically documented cases of PC in the Pachyonychia Congenita Research Registry are dominantly inherited (personal communication with Mary E. Schwartz at the Pachyonychia Congenita Project, 2015). To our knowledge, there are no known cases of autosomal recessive PC with confirmed genetic analysis.

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CORRECTION

Error in Text: In the Case Report titled "Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated β -Blockade," published online September 16, 2015, in *JAMA Dermatology*,¹ there were errors in the Abstract, Introduction, Report of a Case, and Figure 3. Instances of "paclitaxel poliglumex" should have read "paclitaxel". This article was corrected online.

1. Chow W, Amaya CN, Rains S, Chow M, Dickerson EB, Bryan BA. Growth attenuation of cutaneous angiosarcoma with propranolol-mediated β -blockade [published online September 16, 2015]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2015.2554.