Vandetanib therapy is a novel once-daily oral multitargeted tyrosine kinase inhibitor, which is currently used in advanced or metastatic medullary thyroid cancer. Skin toxicities are among the most prevalent adverse events reported with this targeted therapy (e.g. acne-like rash, hand-foot skin reaction, hair changes, and paronychia). In addition, photosensitivity reactions may affect more than one third of treated patients. We report here 2 patients developing photosensitivity reactions with vandetanib therapy, including photoonycholysis. Our patients presented a wide range of phototoxic reactions with exaggerated sunburn reactions solely located to photoexposed areas or hyperpigmentation with visible blue dots. More importantly, both patients concomitantly developed nail changes consistent with type 1 photoonycholysis, which had never been reported so far neither with vandetanib therapy nor with other anticancer-targeted therapies. In addition, histopathologic findings and reflectance confocal microscopy imaging performed in one patient suffering from photodistributed skin hyperpigmentation both strengthen the likelihood of a postinflammatory mechanism. Clinicians should be aware of these underestimated but very characteristic photoinduced adverse events, which can lead to treatment interruption and require very strict photoprotective measures in treated patients.