EMH where $SCF^+/CXCL12^+$ cells were sought for immunohistochemically.

A 64-year-old woman with postpolycythemia vera myelofibrosis was referred to our department for multiple red papules on her torso. She had undergone radiation therapy for splenomegaly 6 months prior. Multiple non-blanchable erythematous, smooth-surfaced papules, 2–3 mm in size, were scattered on the torso and the proximal extremities (Fig. 1a). The complete blood count showed pancytopenia with white blood cells 900/μL (normal range: 2700–8500), red blood cells 2.61×10^6/μL (3.37–4.94), Hb 7.4 g/dL (10.5–14.9), platelets 25×10^3/μL (110–347) and reticulocytes 30.8‰ (7.0–20.0). The skin biopsy from the right arm lesion indicated perivascular oedematous changes and epidermal vacuolar changes. Haematoxylin–eosin (HE) staining revealed perivascular infiltration of lobulated granulocytes, orthochromatic erythroblasts and large blast-like cells (Fig. 1b,c). These infiltrating cellular nests were immunohistochemically positive for the myelomonocytic lineage marker CD33, the erythrocyte marker CD235a and the platelet marker CD61 (Fig. 1d–f). Ectopic cellular nest formation with three haematopoietic lineages led to the diagnosis of cutaneous EMH. Further immunofluorescent analysis of the perivascular stromal cells revealed the co-expression of SCF and CXCL12 (Fig. 1g,h).

Extramedullary haematopoiesis after birth is mostly observed in the liver and spleen, and cutaneous EMH is rarely encountered in the clinical practice.[1] Accordingly, only 30 cases of cutaneous EMH were reported.[6] As most studies on EMH have been conducted on mouse models, little is known about the pathophysiology of cutaneous EMH in humans.[3,5,7] It has been shown in mouse models that $SCF^+/CXCL12^+$ MSC-derived cells in the niche recruit and tether HSCs, which express corresponding receptors for these cytokines CD117 (c-KIT) and CXCR4, respectively.[3,7,8] In line with this concept, we herein identified $SCF^+/CXCL12^+$ cells in cutaneous EMH (Fig. 1g,h). Our observation suggests that the formation of the HSC niche may employ a similar mechanism in human cutaneous EMH.

As indicated by comparison between the bone marrow and the spleen in murine studies, different types of $SCF^+/CXCL12^+$ cells may contribute to the formation of haematologic niche.[4] Further investigations are required to clarify the cellular profile of $SCF^+/CXCL12^+$ cells in cutaneous EMH.

Consequently, we presented a case of cutaneous EMH that harboured $SCF^+/CXCL12^+$ cells. The findings suggest that $SCF^+/CXCL12^+$ cells play a role in the formation of the haematopoietic niche in cutaneous EMH.

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References

1 Roberts AS, Shetty AS, Mellnick VM *et al.* Extramedullary haematopoiesis: radiological imaging features. *Clin Radiol* 2016; 1239–1243.
2 Frenette PS, Pinho S, Lucas D, Scheiermann C. Mesenchymal stem cell: keystone of the hematopoietic stem cell niche and a stepping-stone for regenerative medicine. *Annu Rev Immunol* 2013; **31**: 285–316.
3 Ding L, Saunders TL, Enikolopov G, Morrison SJ. Endothelial and perivascular cells maintain haematopoietic stem cells. *Nature* 2012; **481**: 457–462.
4 Inra CN, Zhou BO, Acar M *et al.* A perisinusoidal niche for extramedullary haematopoiesis in the spleen. *Nature* 2015; **527**: 466–471.
5 Chiu SC, Liu HH, Chen CL *et al.* Extramedullary hematopoiesis (EMH) in laboratory animals: offering an insight into stem cell research. *Cell Transplant* 2015; **24**: 349–366.
6 Miyata T, Masuzawa M, Katsuoka K, Higashihara M. Cutaneous extramedullary hematopoiesis in a patient with idiopathic myelofibrosis. *J Dermatol* 2008; **35**: 456–461.
7 Ding L, Morrison SJ. Haematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. *Nature* 2013; **495**: 231–235.
8 Yamamoto K, Miwa Y, Abe-Suzuki S *et al.* Extramedullary hematopoiesis: elucidating the function of the hematopoietic stem cell niche (Review). *Mol Med Rep* 2016; **13**: 587–591.

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Blurry halos after tattooing (tattoo blowouts): a review of 16 cases

Editor

'Tattoo blowout' (TBO) refers to the diffusion of tattoo inks deep in the hypodermis.[1] Tattoo blowout presents as an asymptomatic, permanent, blurry halo of colour around the tattoo. It is rapidly visible after tattooing, but mistaken initially as a haematoma. It is only weeks after when the tattoo is healed that the customer starts to be concerned. Tattoo's aesthetic results are impaired, and tattooed individuals are usually dissatisfied with the outcomes. Cases are rarely reported in the literature.[1–3] We review here a series of 15 patients with 16 TBO between 2011 and 2018, including four cases reported previously.[3,4] For 93% of the patients (14/15), TBO was the reason for consultation (Fig. 1). Patients were seen either by direct consultation ($n = 2$) or by telemedicine/e-mail consultation with dermatologists ($n = 6$), with patients themselves ($n = 4$) or with tattooists ($n = 3$). Ninety-three per cent (14/15) were young women (median age 30 years, range 19–55). All had a fair skin phototype. Tattoos were mainly located on the upper limbs in 81.2% of the cases (13/16), either on the inner side of the arm (69.3%, 9/13)

or on the forearm (30.7%, 4/13). Other localizations included the cheek, the flank and the tight (Fig. 2). Culprit colours were black (62.75%, 10/16), blue and green in three cases each (18.75%). Of specific interest, one man developed a bilateral TBO on both inner arms[3]; a beautician attempted to tattoo herself a mole on the cheek with a syringe and calligraphy ink, twice within 24 h, and two patients reported painful sensations on the tattooed area. According to patients, abstention or laser removal treatment was recommended. Two patients chose to have a new tattoo made over or around the TBO.

To the best of our knowledge, we report the largest series of TBO after tattooing. The frequency of this side-effect is unknown. In a Danish study,[5] TBO was found in 1.2% of the cases (six of 493 tattoo adverse events). However, mild cases may go unnoticed. Tattooists may correct themselves TBO with a new tattoo cover-up or by tattooing around to reduce its visibility. Only those with visible cosmetic impairment may seek for medical advices. The first cases were reported on the dorsum of the foot as 'blue-foot' phenomenon,[1,2] but TBO can happen elsewhere, mainly on the inner side of the arms as illustrated here. The main hypothesis is that the tattoo artist 'tattooed to deep' and ink leaked out of the dermis. The ink may spread easily within the subcutaneous fat. This hypothesis seems to be confirmed by our findings. The thickness of the epidermis and the dermis varies according to gender and body sites.[6,7] The predominance of young women can be explained by the thickness of the epidermis and the dermis, which is thinner compared to men of similar age group.[6,7] Thicker areas such as the back or sun-exposed areas like the dorsal side of the arms [8] are less prone to TBO. For instance, the thickness of the skin (epidermis and dermis) in the inner side of the arm and the back is 1012 and 1976 μm, respectively.[7] Besides, the inner side of the arm is thicker in men (1192 μm) than in women (828 μm).[7] Additional explanations include gravity (hanging down limbs), tattooist's lack of experience, excessive quantity of ink, tattoo ink chemical properties that would allow it to spread in fatty areas. Tattoos were mostly on flat tint-coloured designs or thick lines. In a few cases, thinner lines could also be responsible of TBO. For patients looking for treatment, TBO laser removal has been reported as efficient.[1,2] Tattooists should be aware of this possible side-effect in areas of thin dermis. Customers, young women with fair skin especially, should be warned about such drawbacks.

Figure 1 Various examples of tattoo blowouts with a colour blurry halo around the tattoos.

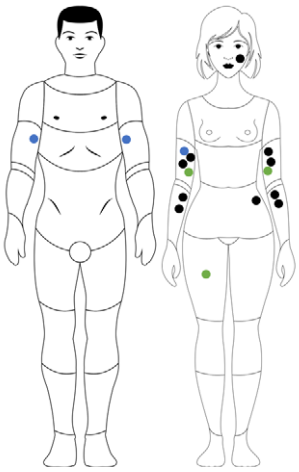

Figure 2 Anatomical distribution of 16 tattoo blowouts according to colours and gender.

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References

1 Molenda MA, Gehris RP, Jukic DM, Obagi S. Blue foot: an unusual complication of tattoo and successful treatment with a QS-Nd:YAG laser. *Dermatol Surg* 2008; **34**: 947–949.
2 Khetarpal S, Molenda M, Seiger E *et al.* Blue foot: a second case of tattoo blow-out pigment spread successfully treated with the QS-Nd:YAG laser. *J Drugs Dermatol* 2010; **9**: 1429–1431.
3 Kluger N. Blurry halos around tattoos: a new case of "tattoo blow-out". *Int J Dermatol* 2014; **53**: e44–e46.
4 Kluger N. Cutaneous complications related to tattoos: 31 cases from Finland. *Dermatology* 2017; **233**: 100–109.
5 Serup J, Sepehri M, Hutton Carlsen K. Classification of tattoo complications in a Hospital material of 493 adverse events. *Dermatology* 2016; **232**: 668–678.
6 Branchet MC, Boisnic S, Frances C, Robert AM. Skin thickness changes in normal aging skin. *Gerontology* 1990; **36**: 28–35.

7 Lee Y, Hwang K. Skin thickness of Korean adults. *Surg Radiol Anat* 2002; **24**: 183–189.
8 Querleux B, Baldeweck T, Diridollou S *et al.* Skin from various ethnic origins and aging: an in vivo cross-sectional multimodality imaging study. *Skin Res Technol* 2009; **15**: 306–313.

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Genetic polymorphism of thymic stromal lymphopoietin in Korean patients with atopic dermatitis and allergic march

Editor

Thymic stromal lymphopoietin (TSLP) is recognized as key cytokine in T helper type 2 (Th 2) cell differentiation and contributes to the pathogenesis of atopic disease.[1] The TSLP gene on chromosome 5q22.1 and atopic cytokine gene on 5q31 are adjacent to each other. Based on their genetic location, it is suggested that the TSLP gene is involved in the progression or activity of atopic disease. Genetic association studies involving TSLP single nucleotide polymorphisms (SNPs) and allergic rhinitis or asthma in different racial group have yielded disparate and inconsistent results.[2–5] Moreover, there is a lack of research concerning the association between TSLP SNPs and atopic dermatitis (AD), especially in Asian people. AD during infancy often preludes the development of allergic rhinitis and asthma in later childhood, the so-called allergic march (AM). One study revealed that epithelial cell-derived cytokine, such as TSLP, might drive the progression from AD to asthma and food allergy.[6] Therefore, it is supposed genetic variants of TSLP affect the progression of AD and AM. We aimed to investigate the association between four possible TSLP polymorphisms and atopic disease in a Korean population.

Four candidate TSLP SNPs observed in Asian atopic patients were selected to carry out Sanger sequencing analysis. Interestingly, rs2289276 and rs2289278 attained statistical significance in the dominant model between the control group and AM group ($P = 0.05$ and $P = 0.0441$, respectively; Table 1). Subjects with the TT or CT genotypes of rs2289276 had a decreased risk of AM (OR 0.5571). Moreover, subjects with the GG or CG genotypes of rs2289278 had a lower risk for AM (OR 0.4848). In the control group and all patients with AD or AM (Table 1), compared with subjects with the AG or AA genotype of rs3806932, those with the GG genotype were negatively associated with allergic disease risk. To find a higher probability of developing AM than AD, we analysed the case group as AM patients with the control group being AD patients. The GG or CG genotypes combined with rs2289278 had a lower risk of developing AM (Table 1). The genotype in patients did not display a meaningful correlation with total IgE level and eosinophil count. In the control group and AD group, three SNPs (rs3806932, rs3806933 and rs2289276) were in strong LD ($D' > 0.90$). In all cross-group comparisons, one haplotype block was found in these SNPs ($D' > 0.90$, $r^2 > 0.6$; Fig. 1, block 1). In case–control association analysis, GTT haplotype frequency of the normal control was significantly higher than the AM group ($P = 0.0308$). Also, GTT haplotype frequency of the normal control was significantly different from the AM group ($P = 0.026$).

Four SNPs used in this Sanger validation have been reported in several Asian studies.[3,4,7–9] Of these, two SNPs (rs3806933 and rs2289276) located in the promoter region of TSLP gene were assessed in functional studies.[3,10] In this study, three SNPs including rs3806933 and rs2289276 were in strong LD value and comprised a single LD block. This association is likely to change promoter activity and enhance AP-1 binding to the regulatory element of TSLP.[3] Regarding the regulation of the functional expression of TSLP cytokine, an SNP to SNP interaction might be a stronger factor than individual SNPs.

Our analysis of TSLP SNPs of Korean AD and AM patients is the first trial. It was verified that three SNPs (rs3806932, rs2289276 and rs2289278) are associated with susceptibility of atopic disease. We found three SNPs (rs3806932, rs3806933 and rs2289276) form one LD block; most especially, it is expected that the GTT haplotype strongly contributes to AM. It is important to see significant potential as a genetic factor in the progression of the AM.

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References

1 Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol* 2010; **11**: 289–293.
2 Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Doi S, *et al.* Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. *Nat Genet* 2011; **43**: 893–896.
3 Harada M, Hirota T, Jodo AI, Hitomi Y, Sakashita M, Tsunoda T, *et al.* Thymic stromal lymphopoietin gene promoter polymorphisms are associated with susceptibility to bronchial asthma. *Am J Respir Cell Mol Biol* 2011; **44**: 787–793.
4 Gao PS, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, *et al.* Genetic variants in thymic stromal lymphopoietin are associated with

