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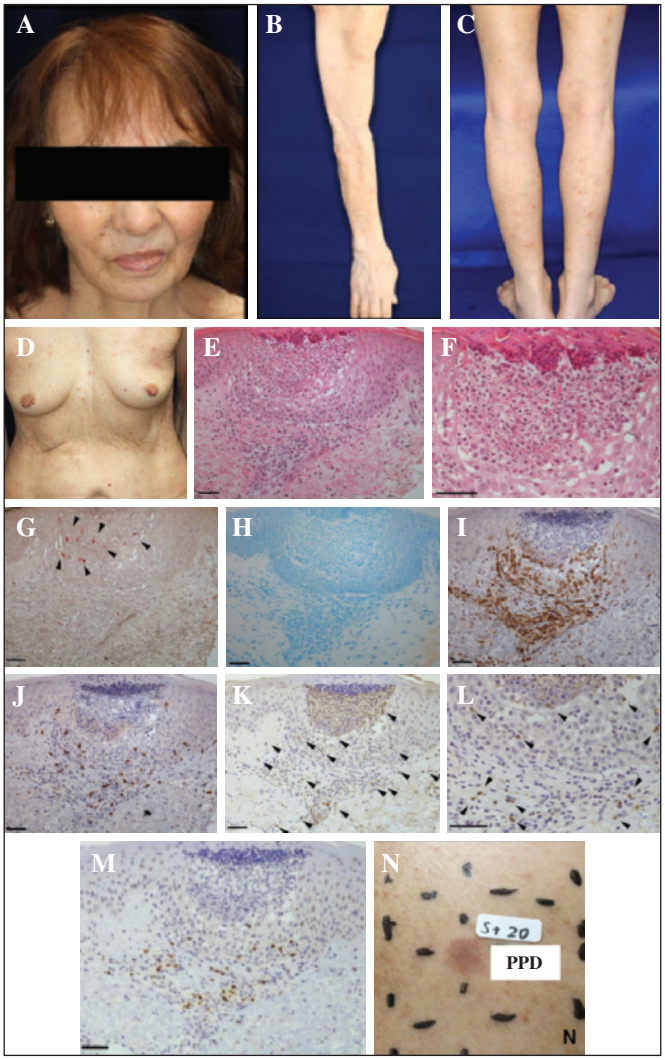

Figure 1. Clinical and histological features of the case. **A**-**D**) The patient with coloured hair (**A**), dry skin, and prurigo-like papules with scratch marks spread over the upper (**B**) and lower (**C**) extremities and trunk (**D**). **E**, **F**) Hyperkeratosis, parakeratosis, acanthosis, and intense neutrophil infiltration beneath the honey cell layer, with lymphocytic infiltration in the lower layer of the epidermis and perivascular and intracollagenous area in the upper dermis (haematoxylin and eosin; x200 [**E**], x400 [**F**)]. **G**) Moderate basophil infiltration (arrowheads) in the neutrophilic micro abscess in the subcorneal layer (new fuchsin; ×200). **H**) Mast cells are not observed around the lesion (toluidine blue; ×200). **I**, **J**) CD4+ (**I**) and CD8+ (**J**) cells in the epidermis and upper dermis (DAB; ×200). **K**, **L**) IL-17+ cells (arrowheads) in the epidermis and upper dermis (DAB; ×200 [**K**], 400 [**L**)]. **M**) Foxp3+ cells in the epidermis and upper dermis (DAB; ×200). Scale bar, 50 μm. **N**) Patch test using the Japanese standard series; erythema is observed in lesion no. 20 (PPD).

A case of prurigo caused by hair dye containing p-phenylenediamine: histopathological findings

p-phenylenediamine (PPD) is a common allergen among hairdressers and hair dye consumers. Delayed-type IV contact hypersensitivity commonly occurs with PPD exposure, manifesting as eczematous eruptions (*e.g.*, erythema, papules, and vesicles) in localised exposed areas, with subsequent systematised presentation in some cases [1]. Contact allergens, including PPD and metals, may be responsible for prurigo as a clinical expression of allergic contact dermatitis [2, 3]. Although common, neither the histopathology nor molecular mechanisms of PPD-induced prurigo have been elucidated. Herein we report a case of prurigo caused by PPD contained in hair dye and show the histopathological features, including the characteristics of an immune cell infiltrate.

A 76-year-old Japanese woman with dyed hair (*figure 1A*) presented with a three-year history of itchy rash on her trunk and extremities that was diagnosed as prurigo nodularis or urticaria in other hospitals. The rash was poorly controlled by oral anti-histamine agents, topical steroids, and anti-IgE antibody therapy. Severe itching left her unable to sleep. Physical examination revealed dry skin and multiple, prurigo-like papules with scratch marks spread over her trunk and extremities (*figure 1B-D*). A biopsy was performed on a papule on her lower extremity. The histopathology exhibited hyperkeratosis, acanthosis, and a subcorneal collection of neutrophils, with

lymphocyte and neutrophil infiltration around vessels and the intracollagenous area in the upper dermis (*figure 1E-F*). Immunohistochemical staining revealed moderate basophil infiltration in subcorneal microabscesses (*figure 1G*), with no mast cells in and around the infiltration (*figure 1H*). Several CD4+ cells were infiltrated beneath the neutrophil infiltration and perivascular area in the upper dermis (*figure 1I*), although CD8+ cells were scarce within this infiltration (*figure 1J*). Moderate interleukin (IL)-17+ cells were infiltrated in and around the microabscesses and upper dermis, among which some cells were segmented leukocytes (*figure 1K-L*). In addition, moderate Foxp3+ cells were observed in this infiltration (*figure 1M*).

Laboratory tests revealed a normal blood count and total serum IgE level. We performed patch tests using a Japanese standard series including PPD, which revealed a positive reaction (+), presenting as an erythema with infiltration for PPD (0.065 mg/81 mm^2 specimen), but a negative reaction for the others allergens (*figure 1N*). Following the diagnosis of PPD allergy, we instructed the patient to discontinue using the hair dye, after which the eruptions gradually improved with steroid ointment without exacerbation. Therefore, this case was diagnosed as prurigo caused by PPD allergy. However, a possible placebo effect from discontinuing the hair dye on elimination of the pruritis was not completely denied.

PPD sometimes induces prurigo in sensitised individuals, and the underlying mechanisms remain unknown [2]. Several studies using different mouse models have revealed potential mechanisms for contact hypersensitivity to PPD. We previously reported that PPD challenge after a sensitisation procedure during which PPD was applied daily induces a Th2 response, including high IgE and increased expression of IL-4 in the skin [4]. In another model, repeated challenges of PPD after applications at five-day intervals induced exocytosis and a neutrophilic infiltrate in the epidermis, in which IL-24 played an important role [5]. Furthermore, repeated application of hair dye including PPD at intervals of two weeks induced the proliferation of IL-17-producing T cells, interferon γ-producing T cells, and regulatory T cells in lymph nodes [6]. In the present case, neutrophil accumulation in the epidermis and moderate infiltration of IL-17+ cells were observed. Therefore, the histopathological findings in our case are similar to those of the latter two reported studies. The expression of IL-17 and Th2 cytokines was increased in skin lesions of prurigo [7]. In our case, IL-17 produced by lymphocytes and segmented cells might have resulted in prurigo reactions.

Insect bites are the most frequent cause of prurigo. The histopathological findings in our case resemble those of tick bites [8]. Basophils migrate to tick bite sites where abundant neutrophils infiltrate and epidermal hyperplasia occurs via mediators [7]. Similarly, basophils were observed within neutrophil infiltration in thickened epidermis in our case. Although basophils are frequently observed in any prurigo subtype, the role of basophils might vary by subtype [9, 10]. Further studies are necessary to reveal the role of basophils in PPD-induced prurigo.

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Dupilumab treatment of prurigo nodularis in an adolescent

Prurigo nodularis (PN) is a skin disorder with multiple stiff, hyperkeratotic, lichenified dome-shaped nodules, mainly manifesting on the arms and legs. The patient's scratching, due to chronic itch, often causes these lesions to be characterized as excoriation. In pathophysiological terms, chronic pruritus is mediated by a convoluted network of neural and inflammatory signals, which also include the role of interleukin-4 (IL-4) and interleukin-13 (IL-13) that can activate small unmyelinated C fibres through their action on IL-4 receptor α (IL-4Rα) [1].

Dupilumab is a monoclonal antibody that can bind IL-4Rα, acting as a receptor antagonist, inhibiting the signalling of IL-4 and IL-13, which are fundamental cytokines in the type-2 inflammation pathway [2]. In addition to its indication as treatment for selected severe asthma cases, this biologic drug is licensed by the European Medicine Agency (EMA) for the treatment of moderate-to-severe atopic