after one cycle of rituximab (follow-up periods: 65, 27 and 13 months). One patient with BP achieved a partial remission and one patient with antilaminin-γ1 pemphigoid, both treatment refractory, achieved full remission after one cycle of rituximab. Two patients with MMP improved after CD20-depleting therapy: one showed a full remission after two cycles, the other patient showed a partial remission after one cycle of therapy. Three patients had a further progression of the disease with a continued inflammation of the ocular mucous membranes despite therapy.

A follow-up assessment of B-cell levels was performed in six patients by detecting CD19+ and CD20+ in peripheral blood via fluorescence-activated cell sorting analysis. We observed a B-cell depletion after rituximab treatment for 9·7 ± 7·3 months.

Tolerability was good in the majority of patients (20 of 22). Two adverse events were observed during B-cell-depleting therapy. One patient developed a rituximab-induced alveolitis 4 days after the second infusion of rituximab, which was treated with intravenous antibiotics and resolved during therapy. In another patient, the second infusion was stopped due to the development of a metallic taste in the mouth.

Our data show that B-cell ablative treatment is safe and effective in controlling recalcitrant courses of autoimmune blistering skin diseases. Moreover, we observed long-term remission in 15 of 22 patients, with an observational follow-up phase of up to 48 months, which is longer than the follow-up phase used in previous studies (Kanwar and Vinay[7] up to 37 months and Gregoriou *et al.*[8] up to 42 months). Our small data series suggests that patients with PV and PF seem more likely to respond to B-cell depletion than patients with MMP. Furthermore, B-cell depletion can also be considered as a treatment option for patients diagnosed with treatment-refractory BP and antilaminin-γ1 pemphigoid, as we observed good clinical efficacy in these patients as well.

Cumulatively, our data support previous reports on clinical efficacy of a B-cell-targeted treatment in different subsets of autoimmune bullous skin disease. Our findings also support the need for a prospective clinical trial to prove that such treatment is not only efficacious and tolerable but also long-lasting. The long remission period strongly suggests that rituximab therapy is a possible curative approach, as the concomitant immunosuppressive medication was reduced and even stopped for several patients. Apparently long-lived plasma cells, which are thought to play a role in many immunological diseases[9,10] and are not affected by immunosuppressive agents, do not seem to play a central role in the pathogenesis of autoimmune blistering diseases.

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Paraneoplastic pemphigus associated with metastatic lymphoepithelioma-like carcinoma originating from the thyroid gland

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Dear Editor, Paraneoplastic pemphigus (PNP) is a rare, life-threatening, autoimmune, mucocutaneous blistering disease associated with underlying neoplasia.[1] A previous review of 163 patients with PNP revealed that the neoplasms commonly associated with PNP are lymphoproliferative tumours, including non-Hodgkin lymphoma (38·6%), chronic lymphocytic leukaemia (18·4%), Castleman disease (18·4%) and benign thymoma (5·5%). Overall, 16% of PNP cases had nonhaematological neoplasms, including tumours with either epithelial (8·6%) or mesenchymal (6·2%) origin.[2] Lymphoepithelioma-like carcinoma (LELC) describes a group of tumours with histological features identical to undifferentiated nasopharyngeal epithelial tumours that occur outside the nasopharynx.[3] Although LELC has been observed in many organs, primary

LELC of the thyroid gland is extremely rare. Cases of LELC of the thyroid gland have been reported using many different terms, such as intrathyroidal epithelial thymoma, carcinoma of the thyroid showing thymoma-like features and carcinoma showing thymus-like differentiation (CASTLE).[4] Here, we report a case of PNP associated with primary LELC of the thyroid gland.

In June 2013, a 59-year-old Korean woman visited our department with a 1-month history of progressive flaccid blisters and erosions on the whole body (Fig. 1a). The patient also presented with painful erosions on the oral and genital mucosae (Fig. 1b). She previously underwent a total thyroidectomy in 2001 due to LELC of the thyroid gland. One year later, a unilateral radical neck dissection was performed due to a recurrent neck mass. However, the neck mass recurred in July 2009 and resection of the salivary gland was performed. On histopathological examination, high-grade LELC was confirmed. In September 2010, intermittent diplopia due to brain metastasis developed and the patient was treated with gamma knife radiosurgery. In July 2012, a computerized tomography scan of the chest showed lung metastasis.

In May 2013, blisters developed over the entire body. A biopsy specimen revealed subcorneal acantholytic blisters (Fig. 1c). Direct immunofluorescence showed IgG deposition along the cell surfaces of keratinocytes (Fig. 2a). Indirect immunofluorescence (IIF) using human skin substrates showed IgG antibodies binding to the surface of keratinocytes at a titre of 1 : 160. IIF using guinea pig urinary bladder showed a weak deposition of IgG antibodies on the epithelia (Fig. 2b). Enzyme-linked immunosorbent assay (ELISA) for antidesmoglein (anti-Dsg) 1 antibodies was positive, but Dsg3 ELISA was negative. Novel ELISA of a mammalian recombinant protein of Desmocollin (Dsc)1–Dsc3 showed negative results. Immunoblotting analysis using human epidermal extracts revealed that the patient's sera reacted with envoplakin (210 kDa) and periplakin (190 kDa) (Fig. 2c). Based on these findings, she was diagnosed with PNP associated with metastatic LELC of the thyroid.

The patient was treated with intravenous dexamethasone (10 mg) and intravenous immunoglobulin (0·4 g kg^{-1} for 5 days), followed by three weekly administrations of rituximab at a dose of 500 mg (375 mg m^{-2}). Two months later, the cutaneous lesions cleared but oral lesions persisted. Despite an improvement in the cutaneous lesions, the patient died of multiple distant metastasis of LELC in September 2013.

The patient was initially thought to have pemphigus foliaceus, because of subcorneal acantholytic blisters and positive

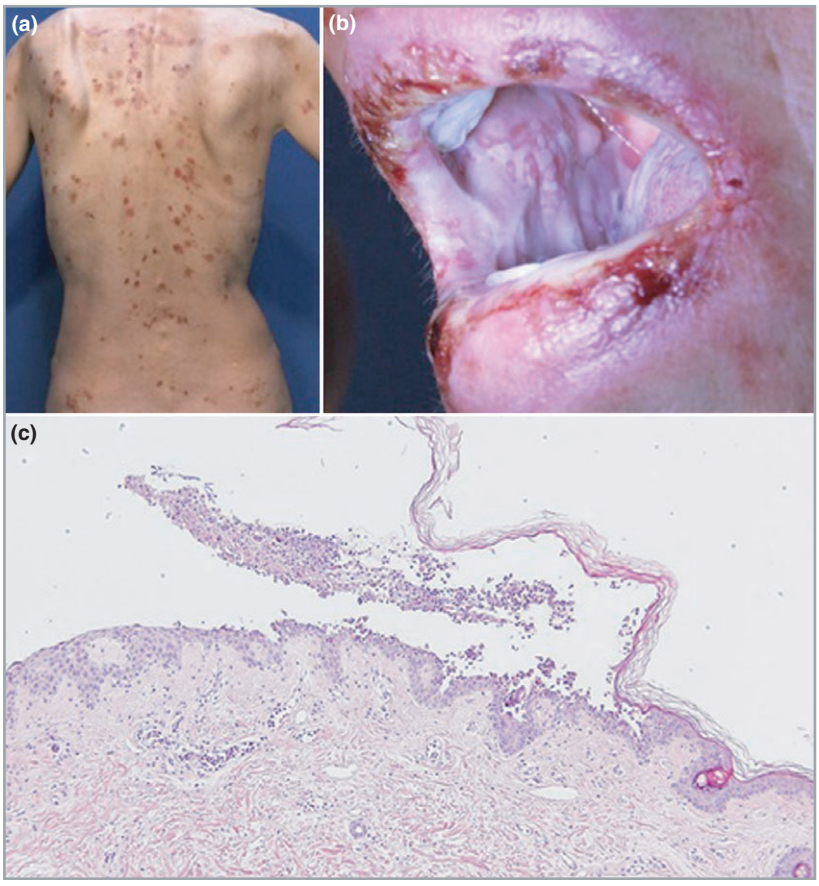

Fig 1. Clinical and histopathological findings. (a) Flaccid blisters and erosions on the whole body. (b) Severe erosions and haemorrhagic crusts on the oral mucosa. (c) Subcorneal acantholytic blisters containing many neutrophils (× 100).

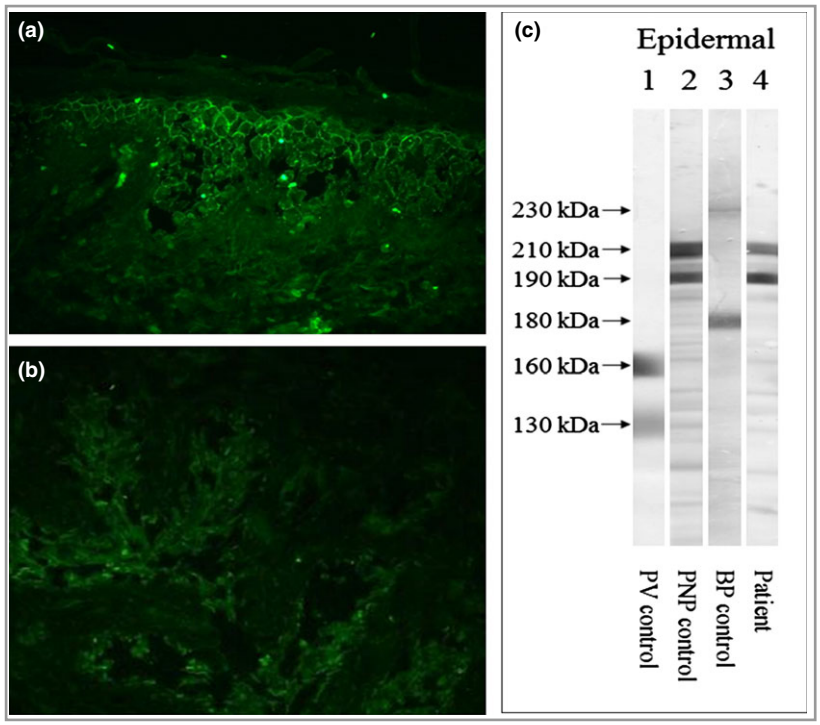

Fig 2. Immunological findings. (a) Cell surface deposition of IgG shown on direct immunofluorescence. (b) A weakly positive IgG deposition on the epithelia of guinea pig urinary bladder shown on indirect immunofluorescence. (c) The results of immunoblotting analysis using human epidermal extracts. Control pemphigus vulgaris (PV) serum reacted with the 160-kDa anti-Desmoglein (Dsg) 1 and 130-kDa Dsg3 (lane 1); control bullous pemphigoid (BP) serum reacted with the 230-kDa BP230 and the 180-kDa BP180 (lane 3); control paraneoplastic pemphigus (PNP) serum and the patient serum reacted strongly with the 210-kDa envoplakin and the 190-kDa periplakin (lanes 2 and 4).

ELISA results only for anti-Dsg1 antibodies. However, severe stomatitis, immunoblotting results with positive reactivity to both envoplakin and periplakin and the presence of underlying neoplasm confirmed the diagnosis of PNP.

Although the majority of patients with PNP reportedly exhibit circulating anti-Dsg3 antibodies, which play a pathogenic role in blister formation, cases of PNP with only anti-Dsg1 antibodies on ELISA have also been reported.[5] The pathomechanisms of oral lesions in PNP remain unclear. They may be more complex than those for classic pemphigus vulgaris, because PNP produces autoantibodies against multiple antigens, including plakin family proteins, Dsgs and Dscs. Additionally, cell-mediated immune responses may also damage mucosal epithelia.[6] It is plausible that mucosal damage due to cellular immune response caused severe oral lesions in our patient, because the patient had only anti-Dsg1 antibodies.

To our knowledge, this is the first case of PNP associated with metastatic LELC originating from the thyroid gland. Primary LELC of the thyroid is a rare malignant neoplasm of the thyroid, showing architectural resemblance to thymic epithelial tumours. LELC of the thyroid is thought to be derived from ectopic thymic tissue or embryonic thymic rest in, or adjacent to, the thyroid.[7] Thirty percent of cases exhibit nodal metastasis, but the prognosis is more favourable than for squamous cell carcinoma or anaplastic carcinoma of the thyroid.[7,8] In general, the course of PNP does not develop in parallel with that of the underlying neoplasm. However, some cases of PNP-associated benign tumours, such as thymoma and Castleman disease, reportedly show favourable prognosis after tumour resection.[1,9]

Although LELC of the thyroid is reported to have a better prognosis than thymic LELC, which is a subtype of high-grade thymic carcinoma, our patient showed multiple brain and lung metastases, which led to a fatal outcome. This case exhibited a rarely aggressive form of LELC of the thyroid, and suggested that LELC of the thyroid gland can be considered to be a PNP-associated neoplasm.

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Acute systemic sarcoidosis complicating ustekinumab therapy for chronic plaque psoriasis

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Dear Editor, Ustekinumab is a human monoclonal antibody, which binds to and inhibits interleukin (IL)-12p40, and is used to treat moderate-to-severe psoriasis and psoriatic arthritis. Sarcoidosis is a systemic granulomatous disease in which IL-12 levels are elevated in tissues, serum and bronchoalveolar lavage samples of affected patients.[1] Therefore, there is a rationale for the use of ustekinumab in treating sarcoidosis. The paradoxical induction of a wide range of autoimmune processes such as lupus erythematosus, vasculitis, sarcoidosis and psoriasis, developing after the initiation of antitumour necrosis factor (anti-TNF) biological therapies, is increasingly being reported.[2]

We present the first reported case, to our knowledge, of sarcoidosis developing in a patient receiving ustekinumab for chronic plaque psoriasis (or indeed any indication).

A 42-year-old white female patient with psoriatic arthritis and severe, difficult-to-control, chronic plaque psoriasis [Psoriasis Area and Severity Index (PASI) 19·3 and Dermatology Life Quality Index (DLQI) 26 at initiation of therapy] had been treated with ustekinumab 45 mg subcutaneously for 14 months when she presented with lethargy, weight loss, night sweats, a dry cough, dyspnoea and painful lesions on the lower legs. Previous treatments included phototherapy, ciclosporin, acitretin, adalimumab and infliximab (both biologics in combination with methotrexate). Methotrexate 20 mg weekly was continued while ustekinumab was initiated.

A good response to ustekinumab was elicited with both PASI and DLQI scores reduced to 1 after 10 months. Methotrexate was gradually reduced over this period and eventually stopped. Occasional naproxen was also taken during this period.

In early January 2013, skin and joint disease remained well controlled using ustekinumab alone. However, 2 months later our patient became acutely unwell, as described above. On examination, tender, erythematous subcutaneous nodules on the lower legs were present, which were consistent with erythema nodosum. Investigations revealed normal serum angiotensin-converting enzyme and adjusted calcium levels. T-SPOT.TB test for tuberculosis was negative. Chest X-ray revealed bilateral hilar lymphadenopathy. High-resolution computed tomography scan of the chest confirmed the presence of hilar lymphadenopathy with prominent pretracheal and subcarinal adenopathy (Fig. 1a,b) with lung windows revealing pulmonary nodules. Induced sputum samples and washings following bronchoscopy exhibited no acid-fast bacilli, with subsequent mycobacterial culture revealing no growth.

A biopsy from a representative lesion on the lower leg revealed a septal panniculitis in keeping with erythema nodosum (Fig. 2a). Mediastinoscopy was performed with histology from an enlarged mediastinal node, revealing a florid, granulomatous lymphadenitis without necrosis (Fig. 2b).

A clinicopathological diagnosis of acute sarcoidosis was made. Ustekinumab therapy was stopped and systemic steroids were initiated. This brought about a gradual clinical improvement in our patient, although her cutaneous psoriasis began to deteriorate.

To our knowledge, this is the first reported case of sarcoidosis developing in a patient being treated with ustekinumab for any condition. A recently published review of the safety of ustekinumab in the treatment of psoriasis did not include the induction of autoimmune disease or specifically mention sarcoidosis.[3] Anti-TNF biological agents used in the treatment of psoriasis are increasingly being utilized in the management of rheumatic and autoimmune diseases. Paradoxically, these agents have also been reported to induce a wide range of these very same conditions, described as a 'double-edged sword' effect of biologics, with over 1500 cases currently

