Table 3 Selection of pair for propensity score matched cohort analysis

Propensity score	DAV-IFN-β	Non-use	Pair selected
Stage II			
0.00086–0.217	0	20	0
0.237–0.561	10	11	10
0.564–0.868	15	6	6
0.910–0.997	19	1	1
Stage III			
0.0077–0.549	4	9	4
0.585–0.899	9	5	5
0.955–0.991	14	0	0
0.992–1.00	14	0	0

Results

Of all the melanoma patients seen at our institute from January 1998 to December 2009, 82 were in stage II and 60 were in stage III. All the studied patients had primary cutaneous melanoma. Patients with mucosal melanoma were not included. During follow-up, 30 (36.6%) stage II and 36 (60.0%) stage III patients had recurrence or metastasis, and 16 (19.5%) stage II and 28 (46.7%) stage III patients died from melanoma. Of all the prematch patients, 44 (53.7%) stage II and 44 (73.3%) stage III patients underwent DAV-IFN-β therapy. In the DAV-IFN-β therapy group, the mean number of treatment cycles was 3.25 (1.26) for stage II and 3.84 (1.48) for stage III. Of the patients who underwent DAV-IFN-β therapy, 23 (52.3%) stage II patients and 25 (56.8%) stage III patients had postoperative IFN-β maintenance therapy (local injection of IFN-β without administration of DAV). The mean follow-up period for all patients was 58.4 (38.9) months. The baseline characteristics of the prematch patients are shown in Table 1.

In the crude comparison, the mean (±SE) estimated disease-free survival rates for stage II were 30.0±21.6% with DAV-IFN-β therapy use and 58.4±9.2% with non-use (hazards ratio for recurrence, 0.87; 95% CI, 0.42–1.81; $P = 0.71$) (Fig. 2a, Table 2). Melanoma-specific survival rates for stage II were 71.1±8.6% with DAV-IFN-β therapy use and 74.5±8.9% with non-use (hazards ratio for death, 0.72; 95% CI, 0.26–1.99; $P = 0.53$) (Fig. 2b, Table 2). Likewise, disease-free survival rates for stage III were 37.8±8.3% with DAV-IFN-β therapy use and 29.2±11.8% with non-use (0.52; 95% CI, 0.25–1.06; $P = 0.070$) (Fig. 2c, Table 2). Melanoma-specific survival rates for stage III were 49.3±9.5% with DAV-IFN-β therapy use and 32.8±12.7% with non-use (0.47; 95% CI, 0.21–1.01; $P = 0.053$) (Fig. 2d, Table 2). Though the disease-free survival rate in each stage was not significantly different, the melanoma-specific survival rate in stage III was close to significantly higher with

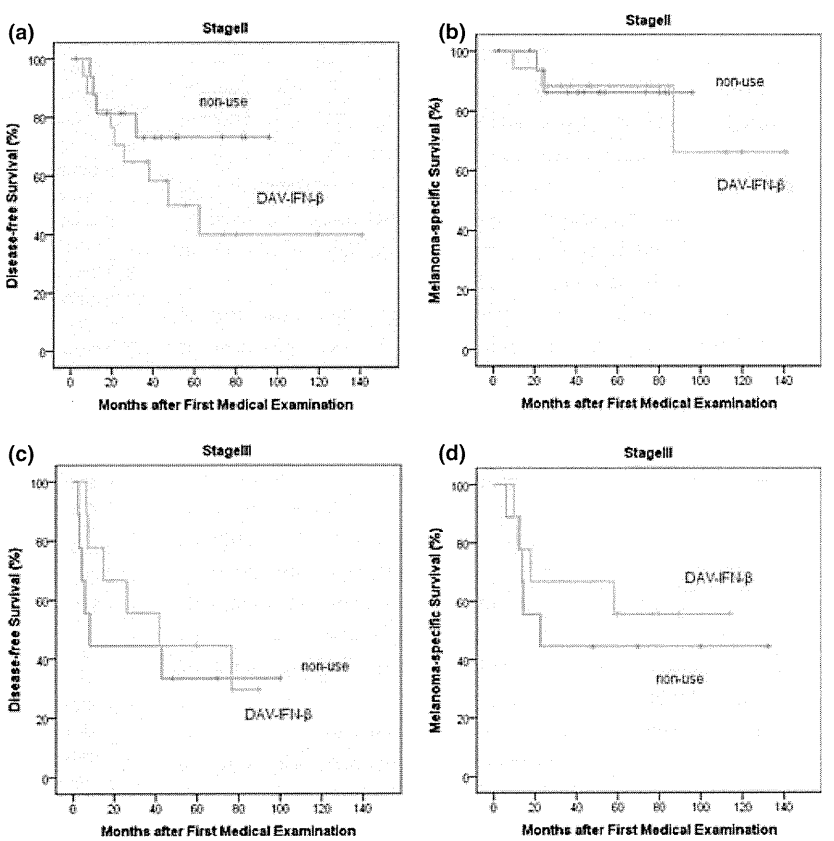

Figure 3 Disease-free survival and melanoma-specific survival in the post-matched patients, using propensity scores. Disease-free survival (a) and melanoma-specific survival (b) in stage II. Disease-free survival (c) and melanoma-specific survival (d) in stage III, respectively. Neither the disease-free survival nor the melanoma-specific survival rate is significantly different between DAV-IFN-β therapy use and non-use in stage II or stage III. Green dots and lines, patients with DAV-IFN-β therapy; blue dots and lines, patients without DAV-IFN-β therapy.

DAV-IFN-β therapy use than with non-use. In the stratified model using propensity scores, no significant difference in survival rates was recognized between DAV-IFN-β therapy use and non-use in either stage II or stage III (hazards ratio for recurrence: 1.74, 95% CI, 0.52–5.77, $P = 0.37$ and 0.55; 95% CI, 0.19–1.55; $P = 0.26$; hazards ratio for death: 1.35, 95% CI, 0.25–7.27; $P = 0.73$ and 0.45, 95% CI, 0.13–1.56; $P = 0.21$, respectively) (Table 2).

Propensity score matching resulted in 17 matched pairs in stage II and nine matched pairs in stage III (Table 3). In the post-matched patients, disease-free survival rates for stage II were 39.9±13.7% with DAV-IFN-β therapy use and 73.1±11.7% with non-use (hazard ratio for recurrence, 2.06; 95% CI, 0.63–6.69; $P = 0.23$) (Fig. 3a, Table 2). Melanoma-specific survival rates for stage II were 66.2±20.0% with DAV-IFN-β therapy use and 86.2±9.1% with non-use (hazard ratio for death, 1.09; 95% CI, 0.17–6.82; $P = 0.93$) (Fig. 3b, Table 2). Likewise, disease-free survival rates for stage III were 29.6±16.4% with DAV-IFN-β therapy use and 33.3±15.7% with non-use (0.69; 95% CI, 0.22–2.17; $P = 0.53$) (Fig. 3c, Table 2). Melanoma-specific survival rates for stage III were 55.6±16.6% with DAV-IFN-β therapy use and 44.4±16.6% with non-use (0.67; 95% CI, 0.18–2.50; $P = 0.55$) (Fig. 3d, Table 2). No significant difference in survival rates was obtained in the patients with DAV-IFN-β therapy use either in stage II or stage III.

Discussion

Chemotherapy is an accepted palliative therapy for stage IV metastatic melanoma,[12–20] and DTIC is the most widely used chemotherapeutic agent for metastatic melanoma.[21] DTIC was originally reported to yield objective responses in up to 25% of patients in older phase II trials, but current large-scale trials with more rigorous criteria have shown response rates of 5–12%.[13,16,17] High-dose IFN-α-2b is the only adjuvant therapy for melanoma approved by the US Food and Drug Administration, although the impact on overall survival is still controversial.[22–25]

The present study was intended to evaluate the contribution of DAV-IFN-β therapy to the improvement of patient prognosis as a postoperative adjuvant chemotherapy. The survival rates of the patients with DAV-IFN-β therapy in the crude comparison at 60-month follow-up were better than those without treatment, similar to the rate of a previously reported study[3] (hazards ratio for death, 0.63; 95% CI, 0.48–0.78, the present study). However, the propensity-score-matched analysis revealed no significant difference between the DAV-IFN-β therapy recipients and non-recipients, either in disease-free survival rates or in melanoma-specific survival rates. Only in the crude comparison for stage III patients, improvement in melanoma-specific survival rates by DAV-IFN-β therapy was almost significant.

This was a single-institute observational study for over a decade. Though propensity score analyses allowed us to replicate some of the characteristics of a randomized controlled trial, they are inherently limited by the number and accuracy of the variables evaluated. In this respect, the numbers of matched pairs in the present study were too small to permit robust conclusions, and we were unable to have an even and a flat population in each stratum that would successfully reduce the deflection between the DAV-IFN-β therapy use group and non-use group. In addition, even after the stratified analysis, other unknown confounders may have affected the outcomes.[26–28]

In conclusion, a propensity-score-matched cohort analysis helps us to reduce bias and gives us a clue to evaluate the efficacy of the therapy. A randomized controlled trial would be required to further define the efficacy and benefit of DAV-IFN-β therapy as a postoperative adjuvant chemotherapy for stage II/III melanoma.

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to be negative for HMB 45, S100, cytokeratin 7, cytokeratin 20, and human papillomavirus polyclonase. There was no proliferation of melanocytes, melanin granules, or erythrocytes in the epidermis, including in the stratum corneum.

Two weeks after the skin biopsy, the pigmentation disappeared spontaneously without treatment, and no further eruptions occurred. Based on the clinical manifestation and characteristic histopathologic features, the diagnosis of pagetoid dyskeratosis was made.

Comment. Pagetoid dyskeratosis is a rare disease, and to our knowledge, only 3 cases with brownish discoloration on the hand have been reported.[1,2] Pagetoid dyskeratosis clinically presents as a brownish macule, and histopathologic findings show pale cells resembling cells of Paget disease within the epidermis. It is speculated that a small portion of the normal population of keratinocytes become these pale cells from reactive proliferation or friction.

Dermoscopy is helpful in the differentiation of melanocytic lesions. The histopathologic findings of proliferation of melanocytes and melanin granules coincide with the brownish dermoscopic findings. Especially in palms and soles, it presents as a pattern of parallel ridges or furrows, and the parallel ridge patterns show high sensitivity (86.4%) and specificity (99.0%) in detecting malignant melanoma. A parallel ridge pattern was detected in 86% of malignant melanoma cases vs in only 1% of melanocytic nevus cases.[3] Parallel ridge patterns were observed in our case, although there were no histopathologic findings of proliferation of melanocytic cells or melanin granules. The thick, wavy, horny cell layer on the skin in the finger regions causes light to be reflected incoherently. The brownish discoloration is presumed to result from the distribution of pale cells along the crista cutis, which triggers further scattered reflection. We conjecture that the lesion's disappearance was the effect of inflammatory responses to the biopsy.

We have reported the first determination of pagetoid dyskeratosis by dermoscopy. In addition to malignant melanomas, other conditions are known to present the parallel ridge pattern under dermoscopy, such as black heel, fixed drug eruptions, and Laugier-Hunziker-Baran syndrome. They can be differentiated by the patient's history, other dermoscopic findings, and histopathologic findings. Pagetoid dyskeratosis can show parallel ridge patterns and should be considered as a differential diagnosis as well.

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Conflict of Interest Disclosures: None reported.

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Paraneoplastic Pemphigus With Anti-Laminin-332 Autoantibodies in a Patient With Follicular Dendritic Cell Sarcoma

To our knowledge, only 4 cases of paraneoplastic pemphigus (PNP) associated with follicular dendritic cell sarcoma (FDCS) have been reported.[1-4] We describe herein a patient with PNP associated with FDCS with anti–laminin-332 autoantibodies.

Report of a Case. A 28-year-old Japanese man presented with a 6-month history of painful erosions on the oral mucosa as well as polymorphic cutaneous lesions including erythemas and erosions (**Figure 1**A). Skin biopsy specimens taken from an erythematous area on the trunk revealed scattered necrotic keratinocytes in the epidermis, vacuolization in the basal layer, and a bandlike lymphocytic infiltration throughout the papillary dermis (Figure 1C). Under the diagnosis of autoimmune blistering disease, the patient had been treated at another institution with immunosuppressive therapies including steroid pulse therapy for 5 months, with no remarkable improvement.

The patient then came to our hospital for evaluation. Indirect immunofluorescence (IF) analysis of a section taken from a healthy area of skin detected IgG antibodies against keratinocyte cell surfaces at a titer of 1:160 but not against the basement membrane zone (Figure 1D). Indirect IF of a rat bladder section detected IgG antibodies against the cell membrane and the cytoplasm of the transitional epithelium at a titer of 1:160 (data not shown). Indirect IF also detected anti–basement membrane zone IgG antibodies reactive with both the epidermal and dermal sides of 1M sodium chloride–split normal human skin section at a titer of 1:40 (Figure 1E). Immunoblot analysis using epidermal extracts as a substrate showed positive immunoreactivity to the 210-kDa envoplakin and the 190-kDa periplakin (**Figure 2**A). Immunoblot analysis using purified human laminin-332 as a substrate showed that IgG antibodies reacted with the 140-kDa and the 105-kDa polypeptides, which are identical to the β3 and the γ2 subunits of the laminin-332 molecules, respectively (Figure 2B). Findings were negative for anti-BP180 antibodies; positive for anti–desmoglein 1 antibodies (index value, 113 [normal, <14]), and negative for anti–desmoglein 3 antibodies by enzyme-linked immunosorbent assay (data not shown).

Computed tomography revealed a 6.4 × 5.7 × 7.7-cm tumor mass in the retroperitoneal area. Histopathologic examination showed typical features of FDCS associated with Castleman disease.

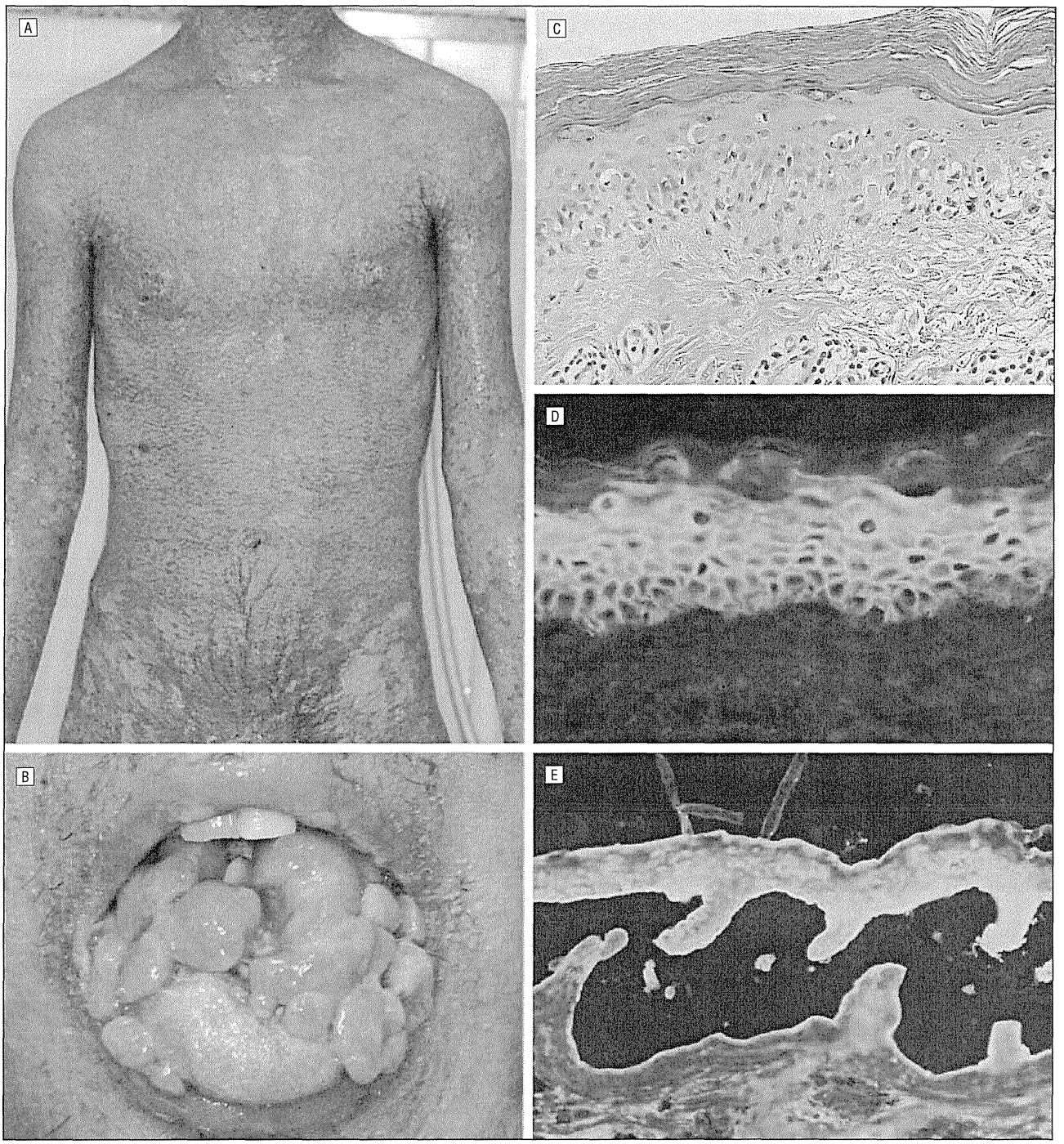

Figure 1. Clinical and histopathological features of the patient. A, Erosions are observed on the whole body. B, Papillomatous hyperplasia on the tongue remains even after skin manifestations have improved owing to tumor resection and postoperative chemotherapy. C, Histopathologic evidence of erosion on the trunk (hematoxylin-eosin, original magnification ×400). D, Indirect immunofluorescence (IF) of normal human skin by circulating IgG of the patient at a titer of 1:160 (original magnification ×400). E, Indirect IF of 1M sodium chloride–split normal human skin by circulating IgG of the patient at a titer of 1:40 (original magnification ×200).

The patient was diagnosed as having PNP associated with FDCS. We could not conclude that he also had anti–laminin-332 mucous membrane pemphigoid. As postoperative adjuvant chemotherapy, the patient received COP therapy (cyclophosphamide, vincristine [Oncovin; Genus Pharmaceuticals], and predonisone) according to the following schedule: intravenous cyclophosphamide, 750 mg/m^2 (day 1) and vincristine, 1.4 mg/m^2 (day 1) every 3 weeks; oral prednisone, 60 mg every day as the initial dose. The skin lesions healed completely except for the papillomatous hyperplasia on the tongue (Figure 1B), although the size of the FDCS lesions in the retroperitoneal area was unchanged.

Comment. To our knowledge, only 1 patient with PNP has been reported to have anti–laminin-332 autoantibodies.[5] Interestingly, that case had 3 malignant neoplasms, including FDCS. Although the malignant tumors

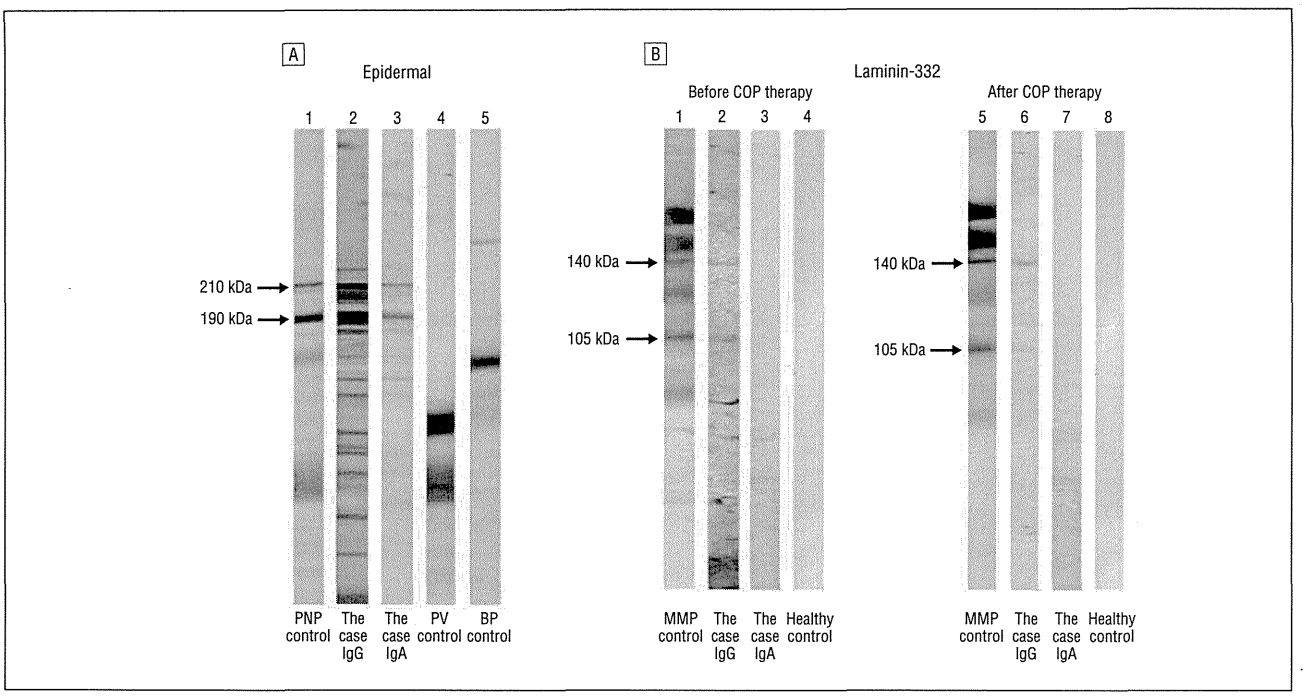

Figure 2. Immunoblot analyses of circulating autoantibodies in the patient's serum performed as described previously.[1,5] A, Results of immunoblot analysis using epidermal extract: control paraneoplastic pemphigus (PNP) serum (lane 1) recognized the 210-kDa envoplakin and the 190-kDa periplakin, which were also detected by IgG (lane 2) and IgA (lane 3) antibodies in the serum of the present patient; control pemphigus vulgaris (PV) serum (lane 4) reacted with the 160-kDa desmoglein 1 and the 130-kDa desmoglein 3; control bullous pemphigoid (BP) serum (lane 5) reacted with the 180-kDa BP180. B, Results of immunoblot analysis using purified human laminin-332 before (lanes 2 and 3) and after (lanes 6 and 7) COP therapy was started (cyclophosphamide, vincristine [Oncovin; Genus Pharmaceuticals], and predonisone). A control antilaminin-332 mucous membrane (MMP) serum (lanes 1 and 5) reacted with the 165-kDa and 145-kDa α3 subunits, the 140-kDa β3 subunit, and the 105-kDa γ2 subunit. IgG antibodies in the serum of the present case (lanes 2 and 6) reacted with the 140-kDa β3 subunit and the 105-kDa γ2 subunit. No specific band was observed for IgA antibodies in the serum of the present patient (lanes 3 and 7) nor for IgG antibodies in serum from a healthy control (lanes 4 and 8).

that induced PNP with anti–laminin-332 autoantibodies were not determined in the earlier case, the facts of the present case together with those of the previous case suggest that FDCS might uniquely induce PNP with anti–laminin-332 autoantibodies.

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Levetiracetam: A Possible New Inducer of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome in 2 Cases

On January 31, 2011, the US Food and Drug and Administration (FDA) registered levetiracetam (LV) on the list of drugs under safety monitoring for the risk of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).[1] Chemically unrelated to aromatic acid antiepileptic drugs, LV is considered a "safe" alternative for patients with previous se-