Supplementary material has been published as submitted. It has not been copyedited, or typeset by Acta Dermato-Venereologica

Appendix S1

Section 1. Source and Rationale for Using Previously Published Clinical Vignettes

All clinical vignettes used in this study were derived from *Hifu no Kagaku* ("The Science of Skin"), a peer-reviewed Japanese dermatology journal. These vignettes included clinical photographs, histopathological images, and accompanying descriptive text, and were used in their original published form without modification. Participants had access to all information, including histopathological findings, whereas the AI system was provided only with clinical photographs and basic clinical information available at initial presentation.

We acknowledge that, because these cases are part of the published literature, prior exposure of the large language model to some of the vignettes cannot be completely excluded. For this reason, the present study is explicitly positioned as a feasibility study focusing on how junior dermatology residents interact with AI-generated diagnostic suggestions, rather than as a definitive evaluation of the standalone diagnostic performance of the AI system.

To address concerns regarding transparency and potential prior exposure, all clinical vignettes presented to the residents are provided in full in this Supplemental Appendix, exactly as they were used in the study. This allows readers to independently assess the characteristics of the cases and to judge any potential influence of prior knowledge on AI output.

Importantly, the primary objective of this study was to evaluate changes in residents' diagnostic decisions before and after exposure to AI-generated differential diagnoses under controlled conditions. Accordingly, the interpretation of the results emphasizes resident–AI interaction and decision-making behavior, rather than absolute diagnostic accuracy of the AI model itself.

Section 2. Participants

Twenty-three dermatology residents (postgraduate year [PGY] 1–4) who were not board-certified dermatologists at the time of the study participated. All participants were actively engaged in routine clinical dermatology practice during the study period.

Participation was voluntary, and all residents completed the assessments individually. No incentives were provided, and participation or performance in the study had no influence on clinical duties or educational evaluation.

Section 3. Presentation of Clinical Vignettes

All 30 clinical vignettes were provided to participants as PDF files. To standardize the evaluation process and minimize cognitive load, the cases were presented in sets of ten, in a fixed order, across three separate sessions. In this design, all participants completed the full set of 30 cases without randomization.

The same clinical images and descriptive information were used for both the initial (AI-unassisted) and subsequent (AI-assisted) assessments. No images or textual descriptions were altered between the two phases, ensuring that any observed differences in diagnostic decisions reflected the influence of AI-generated information rather than changes in case presentation.

Section 4. Information Provided to the AI System

For each vignette, only information that would typically be available at an initial dermatology consultation was provided to ChatGPT-5. Specifically, the AI model received basic patient information (age, sex, and relevant medical history) and clinical findings, including macroscopic descriptions and dermoscopic features of the lesions.

To replicate real-world diagnostic uncertainty, no laboratory data, histopathological findings, or final diagnoses were provided to the AI system. These elements were intentionally withheld so that the AI-generated differential diagnoses were based solely on clinically observable information available at presentation.

All AI outputs were generated using a single, standardized prompt and identical system settings for all cases. No iterative prompting, case-specific modification, or post-generation editing was performed. Details of the prompting procedure are provided in the main manuscript.

Section 5. Conditions for Resident Diagnosis Without AI Support

Before exposure to any AI-generated suggestions, participants were instructed to review each vignette independently and to provide a single most likely diagnosis in free-text format. They were asked to refrain from using any external references (e.g., textbooks, websites, or clinical applications) and to avoid discussion with other participants during the assessment.

No time limit was imposed. Responses were submitted electronically via Google Forms using anonymous identifiers, and all data were collected without personally identifiable information.

Section 6. Conditions for Resident Diagnosis With AI Support

After completing the initial set of diagnoses, participants were presented with three differential diagnoses generated by ChatGPT-5, each accompanied by a brief explanatory description, using the standardized prompting method described in the main manuscript.

Participants then reassessed the same cases in sets of ten, following the identical fixed sequence used in the

AI-unassisted phase, and were instructed to submit a single final diagnosis after reviewing the AI-generated information.

Residents viewed the AI-generated differential diagnoses on their own digital devices (smartphone or personal computer). They were not permitted to interact with the AI system, modify the AI output, or request additional information. No further prompts, follow-up questions, or iterative interactions with the AI system were allowed during this phase.

All revised diagnoses were submitted via the same Google Forms system using anonymous identifiers, ensuring consistency of data collection across both assessment phases.

Section 7. Summary of Workflow

1. Clinical vignettes were delivered in three separate sessions (10 cases per session). Residents independently reviewed each vignette and submitted an initial diagnosis without AI support.
2. After completion of all initial diagnoses, AI-generated differential diagnoses and brief explanatory comments for all 30 cases were provided to the participants.
3. Using the identical three-session structure and the same fixed case order, residents reassessed each vignette and submitted a revised diagnosis after reviewing the AI-generated information.

This two-phase, mirrored workflow ensured consistent exposure conditions across participants and allowed direct comparison of diagnostic decisions before and after AI assistance.

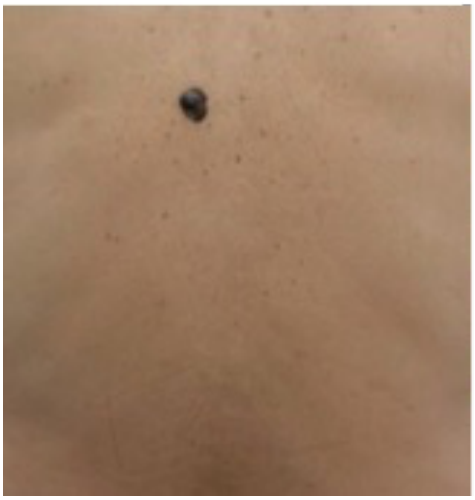
The questionnaire was originally administered in Japanese. For publication, the Japanese items were translated into English, maintaining their original intent.

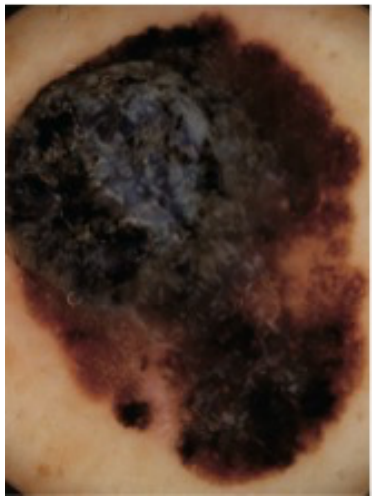
Case 1 – Basic Information and Clinical Findings

Patient: 76-year-old man
Chief complaint: A black nodule on the back

History of present illness:
A black nodule had appeared on the patient's back approximately six months before visiting a previous clinic. Because of its multicolored and asymmetric appearance, malignant melanoma was suspected, and the patient was referred to our department.

Current findings:
A blackish nodule measuring 15.8 × 20.5 mm was present on the back (Fig. 1-1).
Dermoscopy revealed multicolored pigmentation with asymmetric reticular lines, shiny white lines, and areas of structureless black pigmentation (Fig. 1-2).

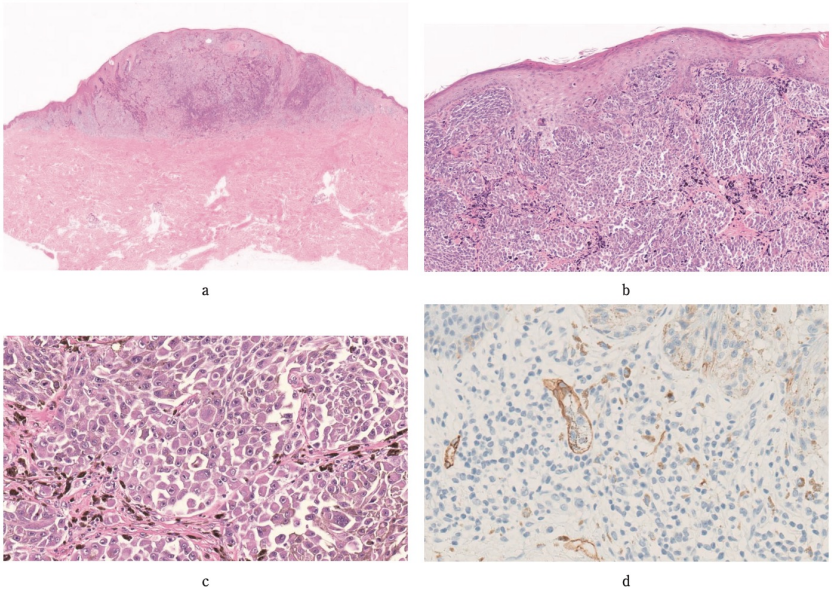




Case 1 – Laboratory and Histopathological Findings

Histopathological examination:
Tumor cells were observed proliferating from the epidermis into the dermis (Fig. 1-3a). At higher magnification, the tumor consisted of atypical melanocytes with pleomorphic nuclei and prominent nucleoli, containing

melanin pigment and proliferating in a sheet-like pattern (Fig. 1-3b, Fig. 1-3c). The tumor thickness was 7 mm. Immunohistochemical staining for D2-40 demonstrated tumor cells within the lymphatic vessels (Fig. 1-3d).



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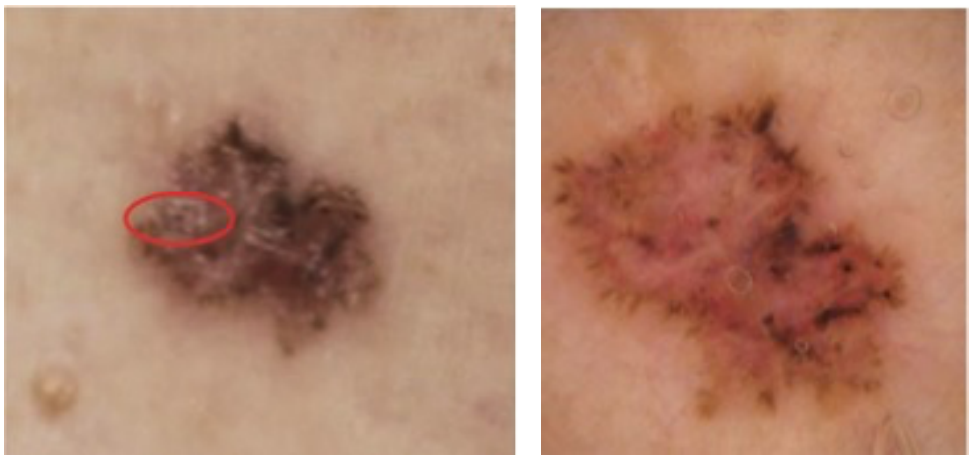
c d

Case 2 – Basic Information and Clinical Findings

Patient: 62-year-old woman
Chief complaint: A slightly elevated blackish-brown nodule on the right cheek

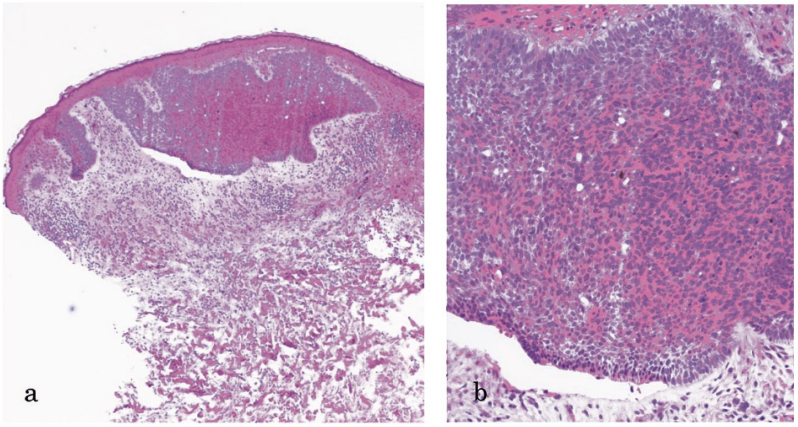
History of present illness:
The patient had been aware of a pigmented lesion on the right neck for several years, with gradual enlargement.

Current findings:
A blackish-brown nodule measuring 10 × 5 mm with slight elevation was present on the right neck (Fig. 2-1). Dermoscopy revealed leaf-like areas and dilated vessels (Fig. 2-2).



Case 2 – Laboratory and Histopathological Findings

Histopathological examination:
A basaloid epithelial tumor continuous with the epidermis was observed in the dermis, with cleft formation between the tumor nests and the surrounding stroma (Fig. 2-3a). At higher magnification, atypical cells with a high nuclear-to-cytoplasmic ratio and melanin deposition were present, showing peripheral palisading (Fig. 2-3b).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Case 3 – Basic Information and Clinical Findings

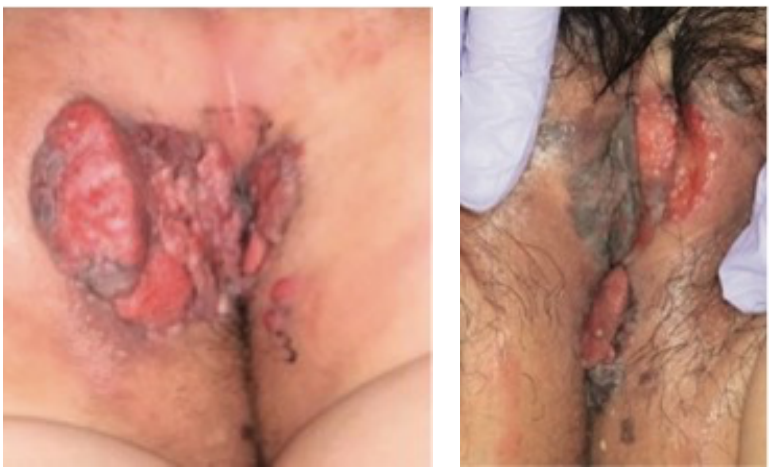
Patient: 30-year-old woman
Chief complaint: A perianal mass

Medical history:
Evans syndrome (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura; status post-splenectomy), neuromyelitis optica, pulmonary embolism, extrahepatic portal vein obstruction, cerebral infarction, and cervical intraepithelial neoplasia.

Medications:
Prednisolone 2 mg and azathioprine 75 mg for neuromyelitis optica (initiated at age 27).

History of present illness:
Warty lesions had appeared around the anus approximately five years prior and were treated with topical imiquimod and electrocautery without improvement. A perianal mass developed one year before presentation and progressively enlarged, prompting referral to our department.

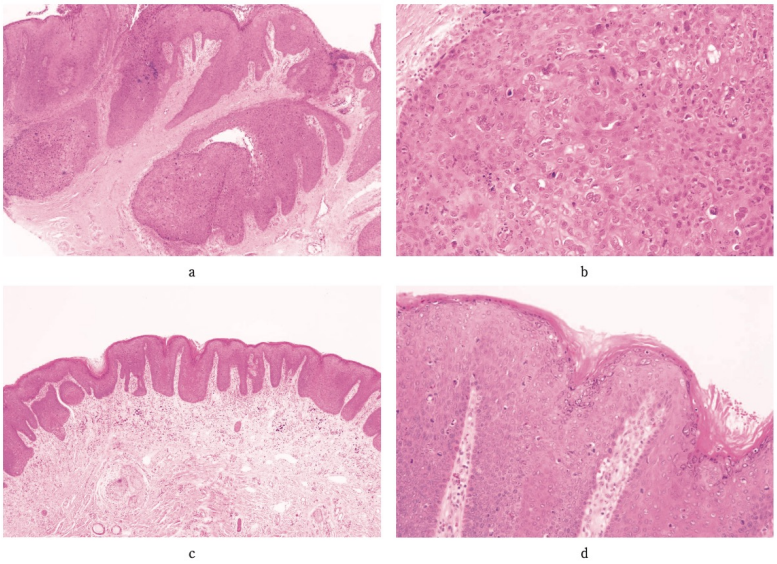
Current findings:
A 3-cm, red, papillomatous mass was observed at the anus. The left labia majora showed a 2.5-cm ulcer with an adjacent 2-cm erythematous slightly elevated lesion. Multiple gray-brown flat papules up to 1 cm were present around the mass (Fig. 3-1).



Case 3 – Laboratory and Histopathological Findings

Laboratory findings:
SCC antigen was elevated at 2.8 ng/mL (reference <1.5 ng/mL). Anti-Dsg1 and anti-Dsg3 antibodies were negative.
Cytology of the lesion was positive for high-risk HPV DNA (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

Histopathological findings:
Biopsy of the perianal mass revealed atypical keratinocytes with large hyperchromatic nuclei and areas of dermal invasion (Fig. 3-2a, 3-2b).
Biopsy of the vulvar pigmented papules showed koilocytosis within the granular layer and abnormal keratinization (Fig. 3-2c, 3-2d).



Case 4 – Basic Information and Clinical Findings

Patient: 33-year-old woman
First visit: October 2009
Chief complaint: A pigmented lesion on the left thigh

Medical history:
No significant past or family history.

History of present illness:
A brownish macule had appeared on the left thigh approximately one year before the first visit and had gradually increased in size.

Current findings:
A 6 × 4 mm brownish macule with irregular borders was observed on the left thigh (Fig. 4-1). Dermoscopy showed brownish pigmentation and irregular dots, but no irregular streaks or blue-whitish veil were identified (Fig. 4-2, Fig. 4-3).

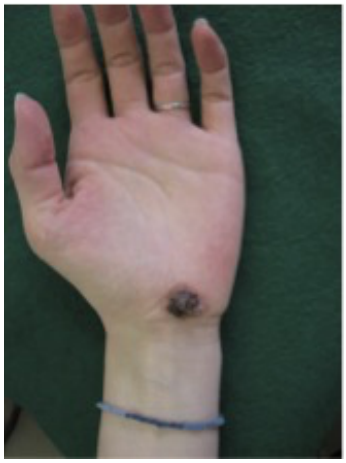


Fig. 1

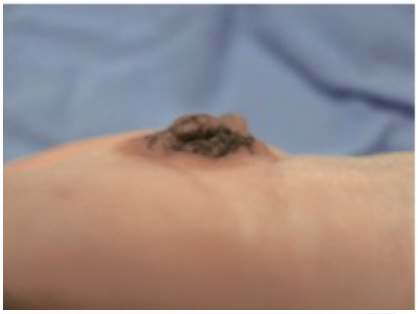
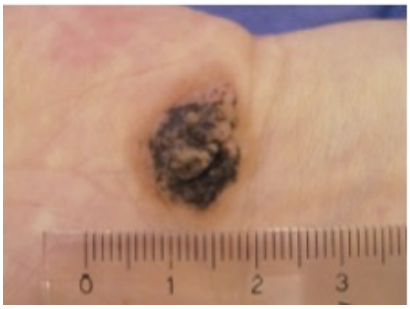


Fig. 2



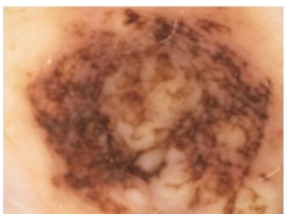
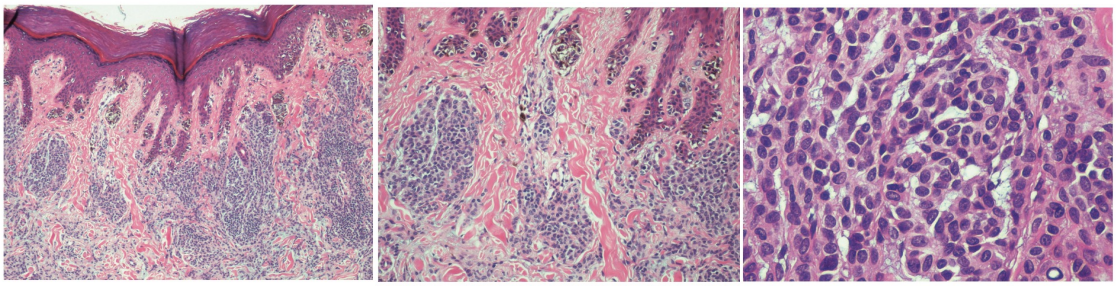


Fig. 3

Case 4 – Laboratory and Histopathological Findings

Histopathological examination:
Atypia of melanocytes within the epidermis was observed (Fig. 4-4). In the dermis, small nests composed of relatively uniform melanocytes were present (Fig. 4-5). The nuclei showed slight size variation but only mild atypia (Fig. 4-6). Immunohistochemical staining for HMB-45 was negative.



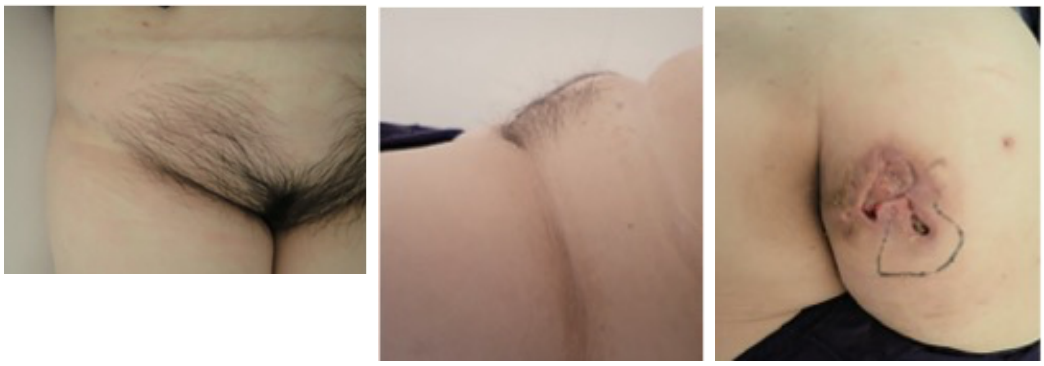
Case 5 – Basic Information and Clinical Findings

Patient: 58-year-old woman
Chief complaint: Subcutaneous tumors of the inguinal and renal regions

Past medical history: Obesity
Family history: Unremarkable

History of present illness:
In 20XX–2, a subcutaneous tumor appeared in the right renal region and gradually enlarged.
She visited a nearby clinic in February 20XX. PET-CT revealed FDG accumulation in the right inguinal region, external iliac lymph nodes, and right renal subcutaneous tissue, raising suspicion for malignant lymphoma.
She was referred to our department for further evaluation.

Current findings:
A subcutaneous tumor measuring 58 × 117 mm and 80 × 40 mm was observed in the right inguinal region (Fig. 1a).
A firm, elastic 36-mm subcutaneous tumor was also noted in the left inguinal region.
The surgical wound in the right renal region had ulcerated and formed a pocket-like cavity (Fig. 1c).
A subcutaneous tumor with induration was present in the inguinal area (Fig. 1b).

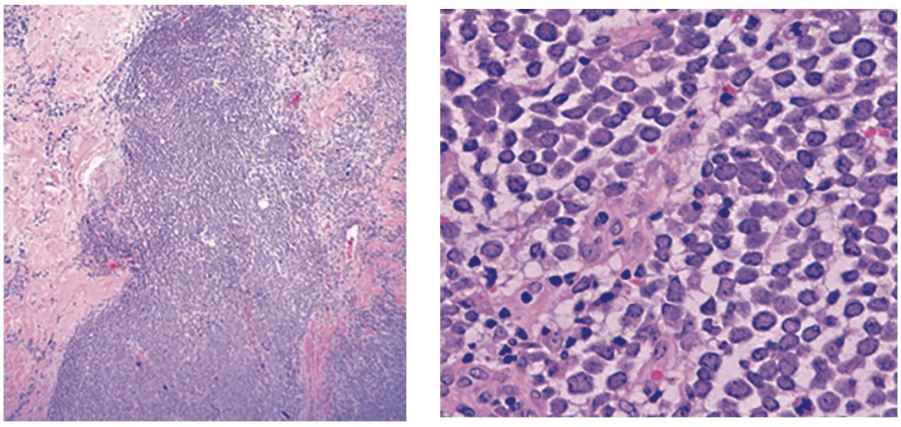


Case 5 – Laboratory and Histopathological Findings

Histopathological examination:

Skin biopsy taken from the right renal subcutaneous lesion revealed atypical round cells with a high nuclear-to-cytoplasmic ratio proliferating from the upper dermis into the subcutaneous adipose tissue (Fig. 2a, b). Some nests of tumor cells showed mitotic figures, and inflammatory infiltrates consisting mainly of lymphocytes were present around the tumor nests.

Immunohistochemistry:
MCPyV: positive (Fig. 3a)
CD8, CK8/18, synaptophysin, chromogranin A: positive
CK20: dot-like positivity around the nuclei (Fig. 3b)
Ki-67 index: ≥ 90 percen



a b

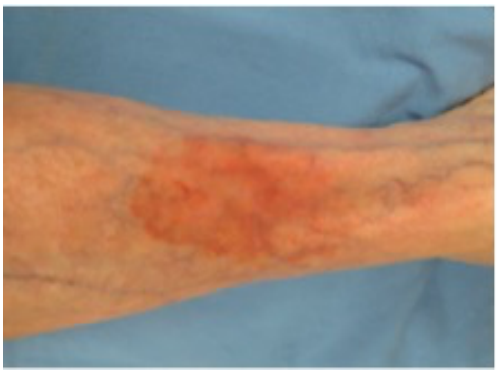
Case 6 – Basic Information and Clinical Findings

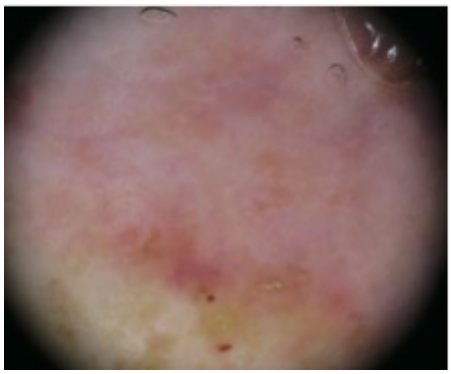
Patient: 96-year-old woman
Chief complaint: Erythematous patch on the right lower leg

History of present illness:
The patient noticed an erythematous patch on the right lower leg approximately three years prior.
She had applied several over-the-counter topical agents without improvement, and the erythematous area gradually enlarged.
She visited a nearby dermatology clinic, where topical steroids were prescribed, but the erythema persisted.
She was referred to our department for further evaluation.

Current findings:
A slightly ill-defined, ovoid erythematous patch measuring 55 × 38 mm with fine scaling was observed on the right lower leg (Fig. 1).

Dermoscopy:
On a whitish to pale pink background, dotted vessels, glomerular vessels, and thin scaling were observed (Fig. 2).



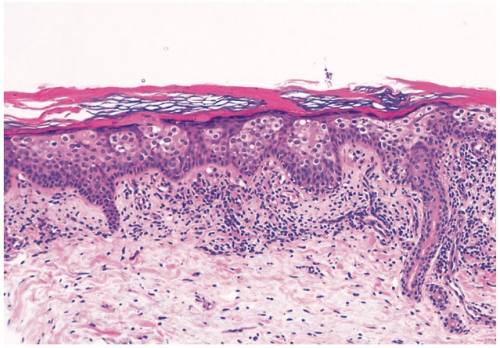


Case 6 – Laboratory and Histopathological Findings

Histopathological examination:
Skin biopsy revealed large pagetoid cells with atypical round nuclei in the epidermis, along with abnormal

keratinocytes.
Foci of parakeratosis were partially observed in the stratum corneum, and lymphocytic infiltration was present in the upper dermis (Fig. 3a, b).

Histochemical and immunohistochemical staining:
PAS staining: positive (Fig. 4a)
Alcian blue staining: negative (Fig. 4b)
AE1/AE3: positive (Fig. 4c)
CK5/6: positive (Fig. 4d)
p63: positive (Fig. 4e)
CK7: negative (Fig. 4f)
GCDFP-15: negative (Fig. 4g)
S-100: negative
CEA: negative



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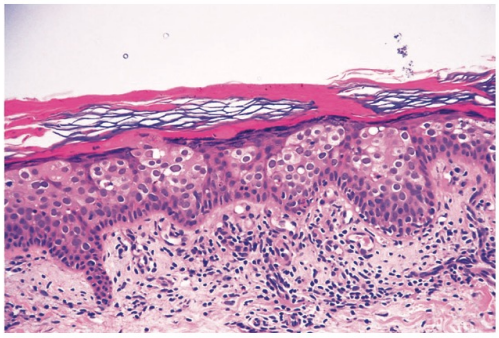

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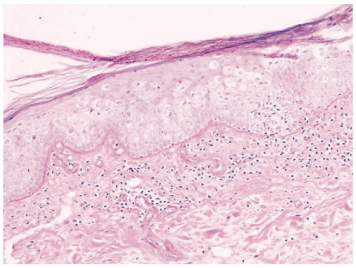

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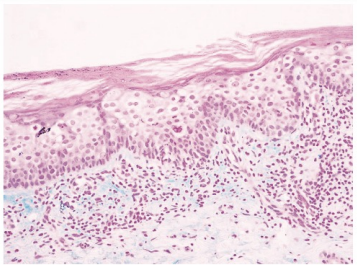

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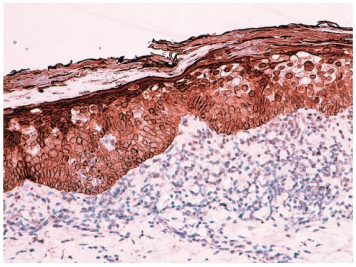

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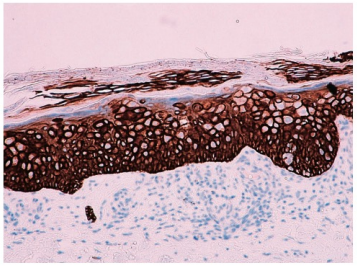

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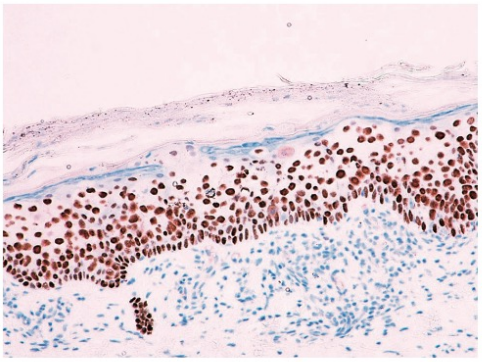

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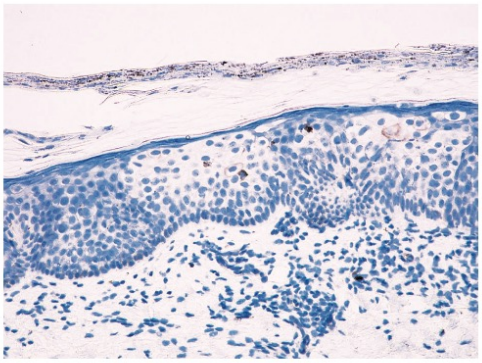

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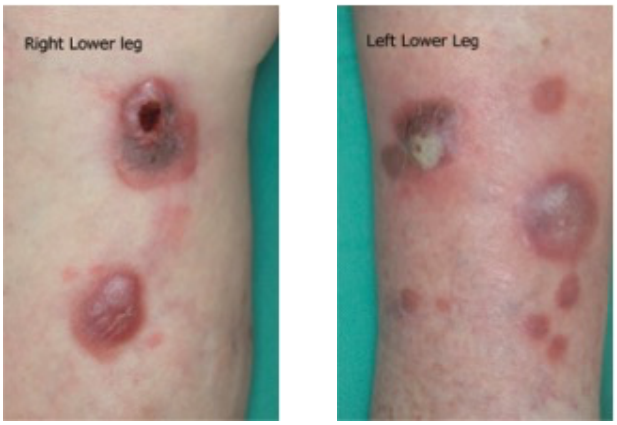
Case 7 – Basic Information and Clinical Findings

Patient: 91-year-old man
Chief complaint: Multiple tumors on both lower legs.

History of present illness:
Around June of year X, the patient noticed nodular lesions on both lower legs. Some lesions gradually developed ulceration, and he was referred to our department in July of year X. He had no notable family history.

Current clinical findings:
Multiple elastic-hard, reddish nodules with well-demarcated borders were present on the bilateral lower legs. Some showed ulceration and crusting (Fig. 1a, 1b).



Case 7 – Laboratory and Histopathological Findings

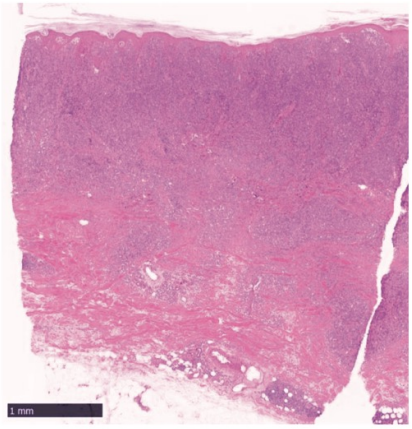
Clinical laboratory findings:
Routine blood tests showed no significant abnormalities except mild elevation of sIL-2R. EBV markers indicated past infection.

CBC: WBC 5,000/μL, Neutrophils 56.6%, Lymphocytes 33.3%, RBC 3.86 ×10^6/μL, Hemoglobin 12.8 g/dL, Platelets 155 ×10^3/μL.
Biochemistry: BUN 17 mg/dL, Creatinine 0.90 mg/dL, AST 17 U/L, ALT 8 U/L, LDH 166 U/L, sIL-2R 628 U/mL.
EBV antibodies: VCA-IgG ×320, VCA-IgM ×10, EBNA ×40, CMV-IgG 250 AU/mL, HTLV-1 ×16.

Histopathological findings (skin biopsy):
The dermis showed dense infiltration of atypical large lymphoid cells with irregular nuclei and prominent nucleoli. Frequent mitotic figures were observed (Fig. 2a, 2b). No epidermal involvement was identified.

Immunohistochemical findings:
Tumor cells were positive for CD20, BCL2 (Fig. 3a), MUM1 (Fig. 3b), and c-MYC (Fig. 3c).
They were negative for BCL6 (Fig. 3d), CD3, CD4, CD5, CD7, CD8, CD10, CD30, and EBER-ISH.

Additional diagnostic findings:
PET-CT demonstrated FDG-avid lesions in both lower legs (SUVmax 18.6), the nasal cavity (SUVmax 10.6), and several lymph-node regions. Biopsy of the nasal cavity lesion revealed DLBCL, consistent with the cutaneous findings (Fig. 4, Fig. 5). Immunophenotype of the nasal lesion: BCL2 positive, BCL6 positive, MUM1 positive, CD10 negative, EBER negative.



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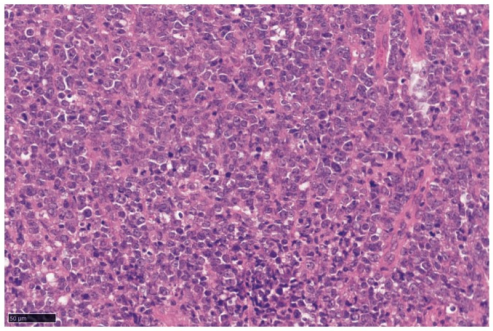
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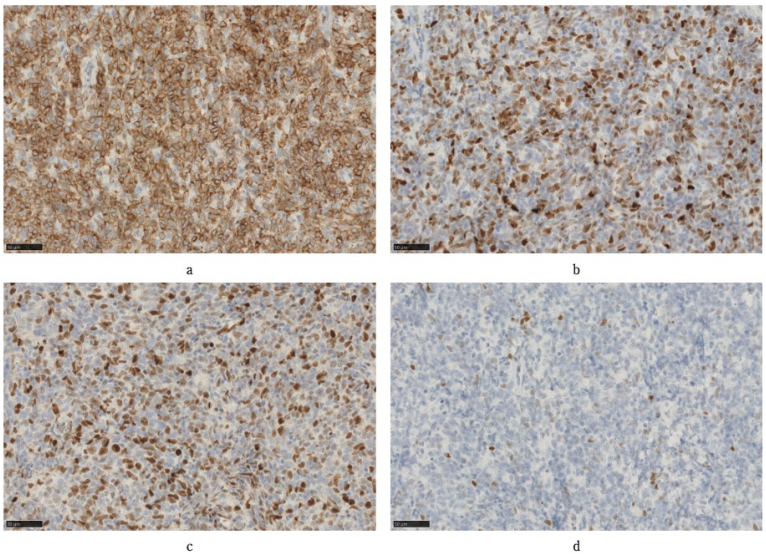

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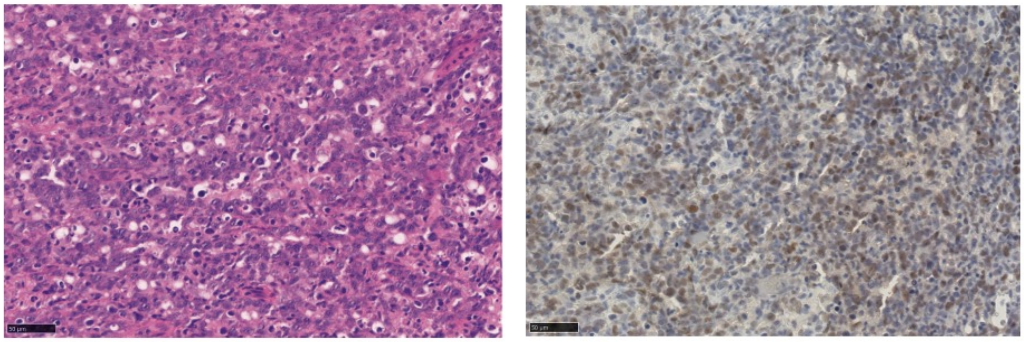


Case 8 – Basic Information and Clinical Findings

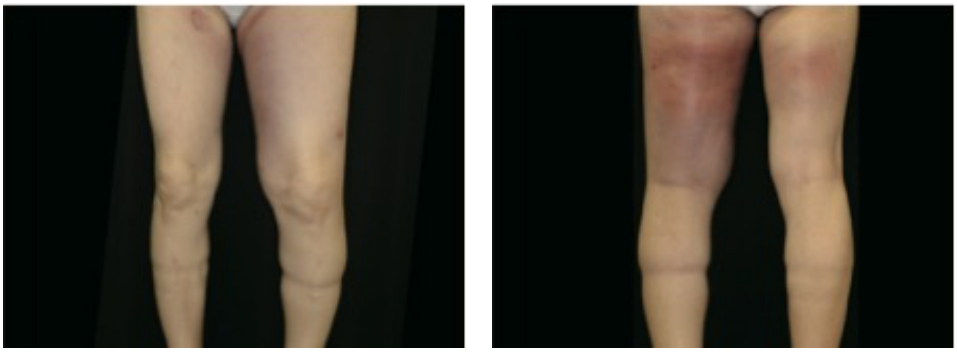
Patient: 61-year-old woman

Clinical course:
Approximately five weeks before her initial visit, the patient noticed an erythematous lesion on the left thigh resembling an insect bite. Over-the-counter topical medications were ineffective, and the erythema gradually expanded with associated swelling, warmth, and pain. She later developed facial swelling, thickened neck skin, and a fever of 39°C. She was evaluated by a local dermatologist and began oral and topical antibacterial treatment, but her symptoms did not improve.

She then presented to a general hospital, where ceftriaxone sodium and hydrocortisone were initiated. Although her liver dysfunction improved, fever and suspected insect-related bacterial infection persisted, and she received additional intravenous minocycline hydrochloride and clindamycin phosphate for three weeks without clinical improvement. She was subsequently referred and transferred to our department for further evaluation.

Past medical history: Right breast cancer surgery at age 58.
Social history: Employee at a large commercial facility; smokes 5 cigarettes/day × 25 years (ages 22–50).

Current clinical findings:
Body temperature was 36.5°C (she had taken antipyretics). She exhibited general malaise and right thigh pain. Physical examination revealed tenderness and induration on the medial and lateral aspects of the left thigh, as well as erythema with induration on the anterior and posterior thigh. Mild erythema with induration was also observed on the right elbow and knee regions (Fig. 1a, b).

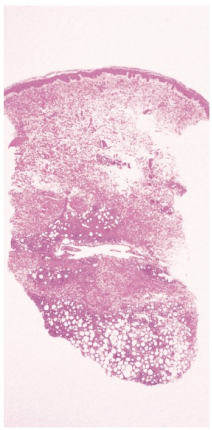


Case 8 – Laboratory and Histopathological Findings

Histopathological examination (skin biopsy):
Hematoxylin–eosin staining demonstrated lobular panniculitis with atypical lymphoid cell infiltration in the subcutaneous lobules, with minimal septal involvement (Fig. 2a, b).
Atypical lymphocytes showed rimming around adipocytes (Fig. 2c).
Immunohistochemistry showed CD3(+), CD8(+), TIA-1(+), granzyme B(+), CD4(–), CD20(–), CD56(–), and EBER-ISH(–) (Fig. 2d).

Genetic study:
Southern blot analysis revealed no TCRγ gene rearrangement.

Laboratory findings at presentation:
WBC 1,700/μL (Neut 70.9%, Lymph 27.4%, Mono 1.1%, Baso 0.6%)
RBC 3.28 × 106/μL, Hb 10.9 g/dL, PLT 254 × 103/μL
AST 210 U/L, ALT 119 U/L, LDH 889 U/L, TP 6.6 g/dL, Alb 2.8 g/dL
BUN 9 mg/dL, Cr 0.53 mg/dL, Na 138 mEq/L, K 3.7 mEq/L, Cl 100 mEq/L
CRP 3.52 mg/dL, IL-2 receptor 1,710 U/mL, ferritin 2,327 ng/mL
Autoantibodies: ANA ×10, anti-VCA-IgM ×10, anti-VCA-IgG ×80, anti-EBNA ×10, anti-EA-DR IgG ×10
T-SPOT negative.



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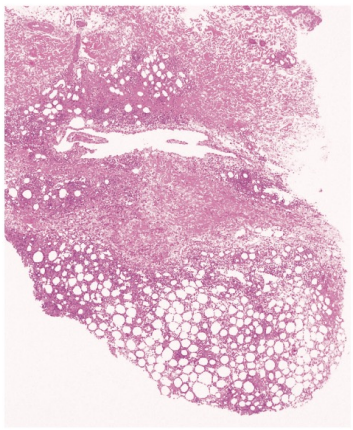

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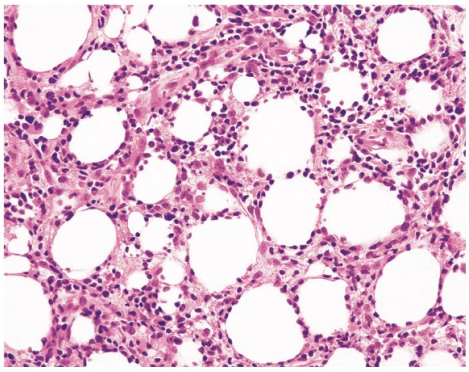

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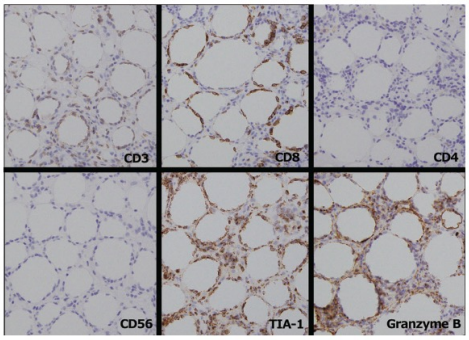

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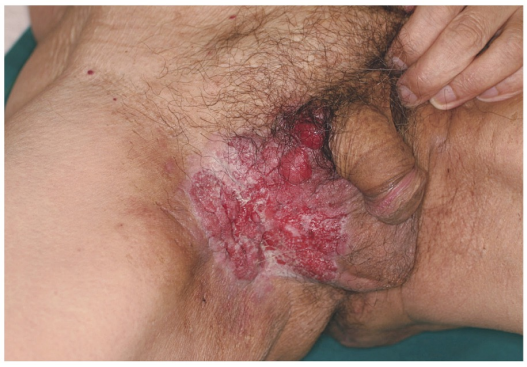
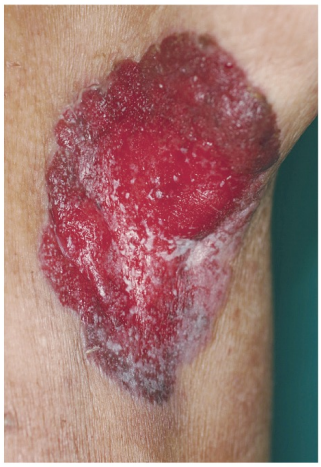
Case 9 – Basic Information and Clinical Findings

Patient: 83-year-old man
Chief complaint: Recurrent erythematous plaques of the inguinal and axillary regions

History of present illness:
The patient had noticed erythematous lesions in the right inguinal and left axillary regions since spring of Year X–1, but because they were asymptomatic, he did not seek medical attention. The lesions gradually enlarged, and topical treatments prescribed by a local clinic were ineffective. He visited our department on August 19, Year X.

Initial clinical findings:
A well-demarcated, moist erythematous plaque with erosions measuring approximately 8 × 6 cm was observed from the right inguinal region extending to the scrotal area (Fig. 1). Part of the lesion appeared crusted. A bean-sized lymph node was palpable in the right inguinal region.
A similar erythematous plaque measuring approximately 6 × 4 cm was observed in the left axillary region, with surrounding blackish pigmentation forming a marginal ridge (Fig. 2). A bean-sized lymph node was also palpable in the left axilla. No obvious scrotal or penile hair loss was noted.





Case 9 – Laboratory and Histopathological Findings

Histopathological findings:
Biopsy of the right inguinal lesion revealed atypical proliferation of large epithelial cells arranged in nests within the epidermis and dermis (Fig. 3, Fig. 4).

Biopsy of the right inguinal nodule showed tumor cells with abundant eosinophilic cytoplasm forming solid nests (Fig. 5).

Immunohistochemical findings:
Immunohistochemistry demonstrated strong HER2/erbB2 membrane positivity in tumor cells (Fig. 6).

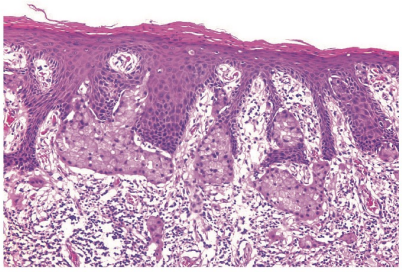


Fig. 3 Histopathological Finding of the Right Inguinal Region (H・E stain ×100)

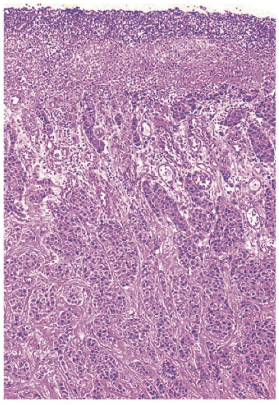


Fig. 4 Histopathological Finding of the Right Inguinal Nodule (H・E stain ×40)

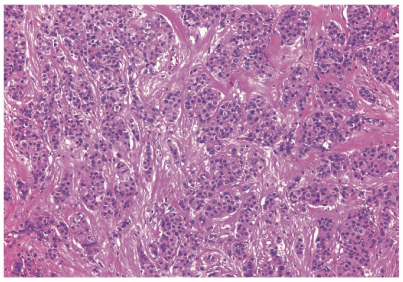


Fig. 5 Histopathological Finding of the Right Inguinal Nodule (H・E stain ×100)

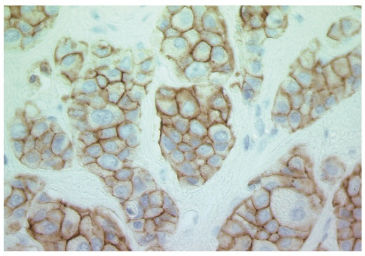
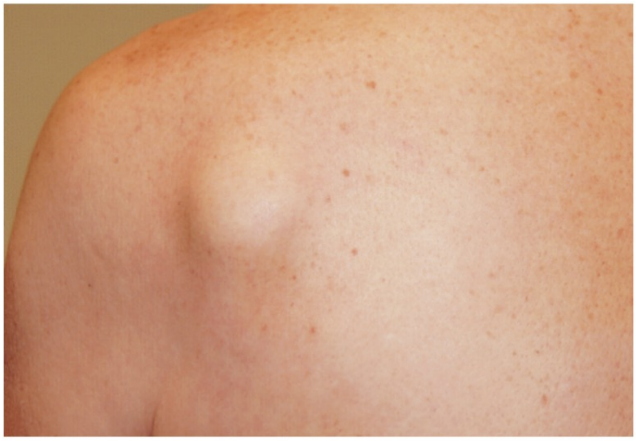


Fig. 6 Immunohistopathological Finding of the Right Inguinal Nodule (erbB-2 protein stain ×400)

Case 10 – Basic Information and Clinical Findings

Patient: 75-year-old man
Chief complaint: Subcutaneous tumor of the back

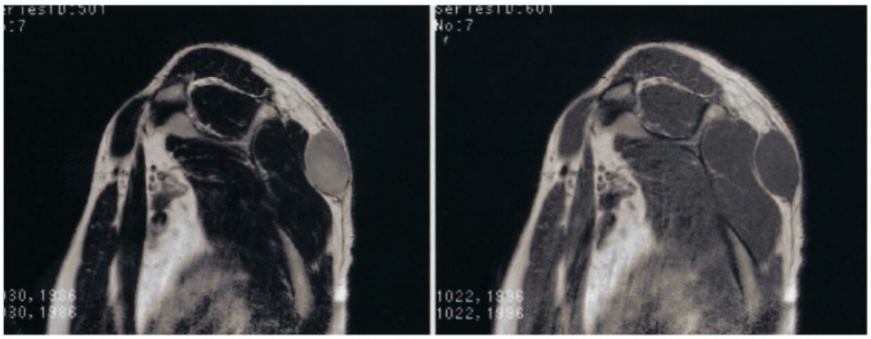
History of present illness:
Approximately two weeks before presentation, the patient's wife noticed a subcutaneous mass on his back. He visited a nearby clinic and was referred to our department on June 6.
On examination, an elastic-hard, poorly mobile subcutaneous tumor with slight surface erythema was observed on the left upper back. No superficial lymphadenopathy was detected (Fig. 1).



Case 10 – Laboratory and Histopathological Findings

Laboratory findings:
Hematologic and biochemical tests showed no abnormalities.

Imaging studies:
MRI revealed a subcutaneous mass measuring approximately 3.3 × 2.2 cm. The mass demonstrated low signal intensity on T1-weighted imaging and slightly high signal intensity on T2-weighted imaging (Fig. 2). Ultrasonography showed a well-circumscribed hypoechoic lesion within the subcutaneous fat layer. Color Doppler imaging demonstrated no significant internal blood flow.

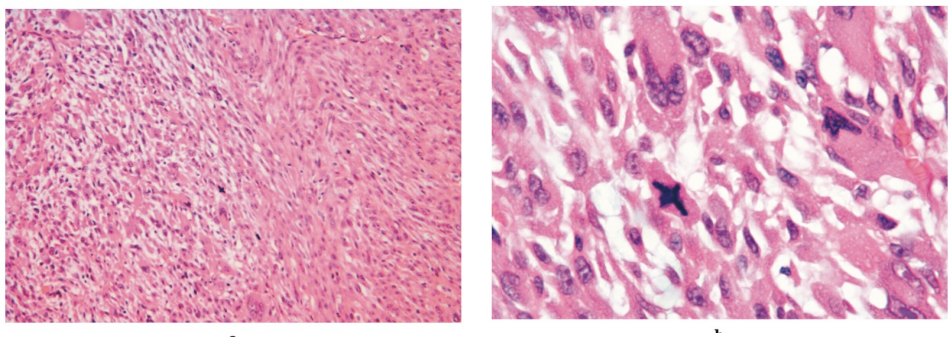


T2 T1

Histopathological findings:

The excised tumor (approximately 3.5 × 2.5 cm) consisted of a well-demarcated proliferation of spindle-shaped atypical cells within fibrous stroma. The tumor cells had elongated nuclei with small nucleoli, and mitotic figures were occasionally observed (1–3 per high-power field). Large atypical multinucleated cells were also seen. No necrosis was identified.

Immunohistochemistry showed positivity for alpha-SMA and vimentin, weak positivity for HHF35, and negativity for desmin. These findings indicated that the tumor was confined within the fibrous capsule (Fig. 4).



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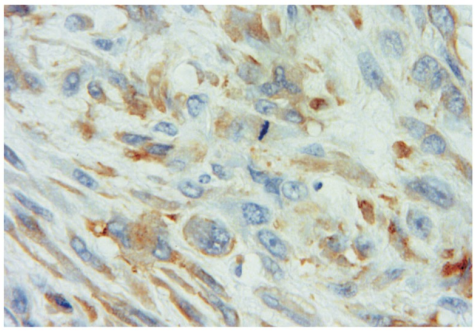

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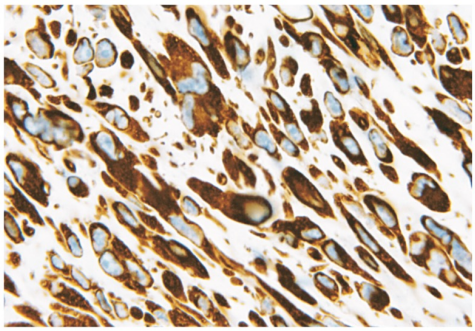

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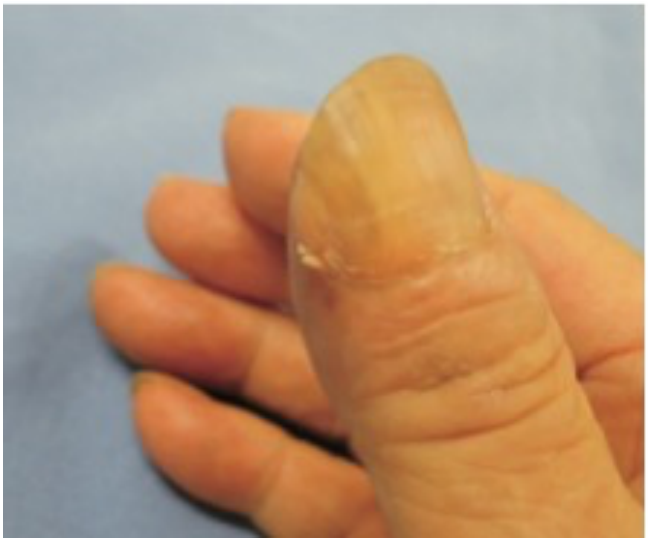
Case 11 – Basic Information and Clinical Findings

Patient: 78-year-old man
Chief complaint: Pain and discoloration of the right thumb accompanied by a small tumor

History of present illness:
In January 20XX, the patient noticed pain and discoloration of the right thumb. As symptoms did not improve, he was referred from a nearby dermatology clinic.

On initial examination, a 10 × 3.5 mm, yellowish-white, elastic-hard nodule was observed on the radial side of the right thumb nail fold. No subcutaneous induration was detected (Fig. 1).



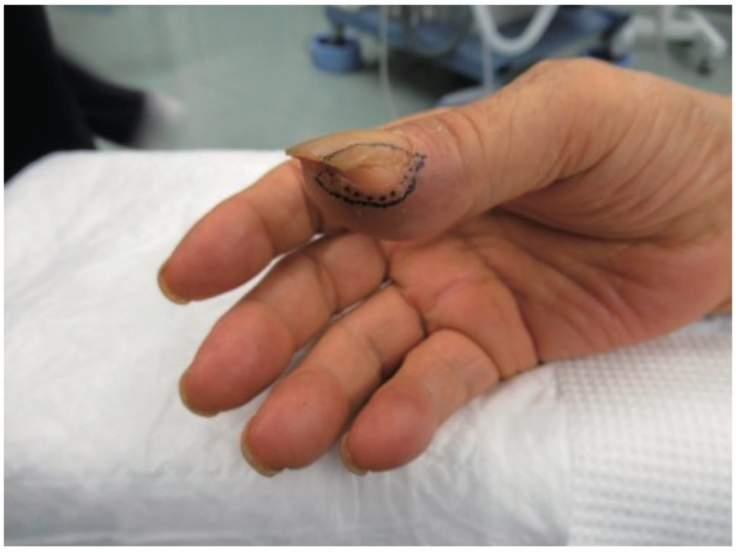
Case 11 – Diagnostic and Histopathological Findings

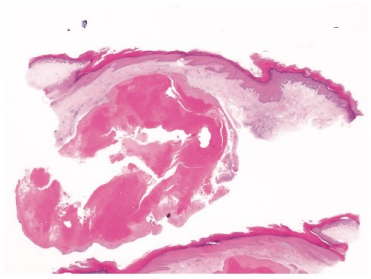
Treatment:
Partial nail plate removal was performed, and the tumor was excised with a spindle-shaped incision along its margin for complete resection (Fig. 2).

Histopathological findings (total excision specimen):
Squamous eddies were scattered throughout the tumor, which was covered by stratified squamous epithelium. Keratinous material was present within the tumor cavity (Fig. 3a–c). No basaloid cell nests, keratin pearls, dyskeratosis, clear cells, or bird-eye structures were observed. No findings suggestive of HPV infection were identified. Nuclear atypia was minimal, and mitotic figures were rare.

Immunohistochemistry:

p16 showed nuclear and cytoplasmic positivity, but the staining pattern suggested nonspecific background uptake, and thus was considered falsely positive. HPV type 16 testing using Anti-HPV16 L1 antibody (rHPV16L1/1058, Abcam, Cambridge, UK) was negative (Fig. 4a, b).





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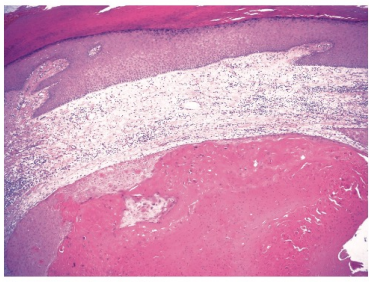

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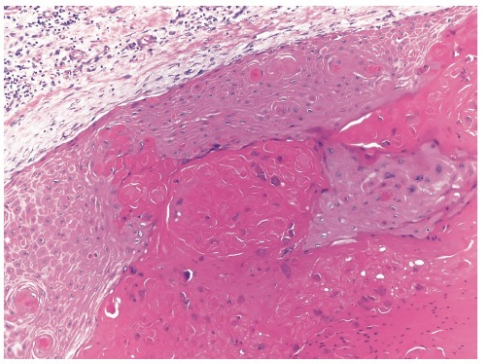

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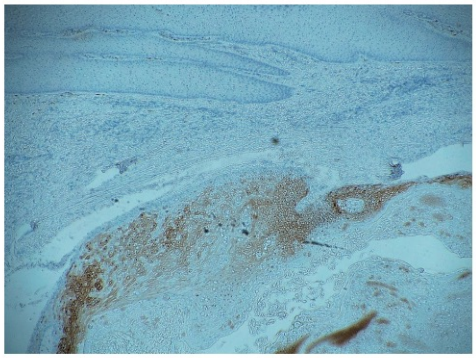

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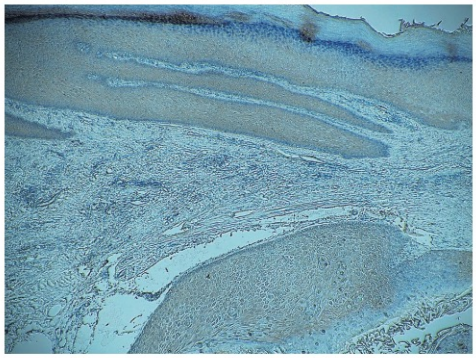

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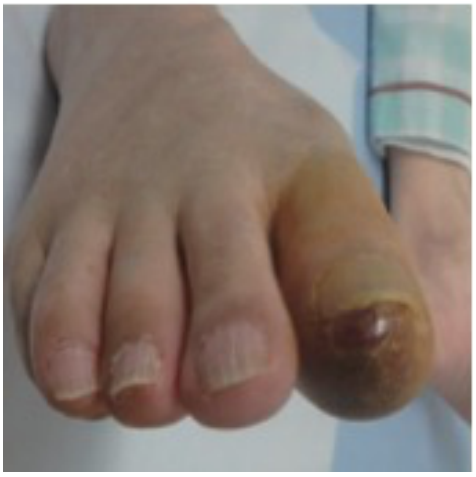
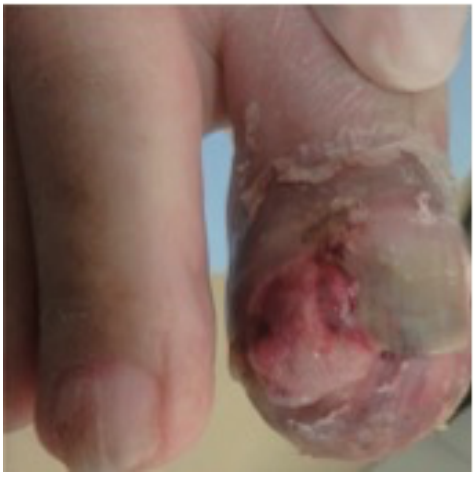
Case 12 – Basic Information and Clinical Findings

Patient: 75-year-old man
Chief complaint: Pain and swelling around the right great toenail
Past medical history: Undergoing chemotherapy for lung squamous cell carcinoma (cT4N2M1a)

History of present illness:
In mid-March 20XX, the patient noticed swelling of the right great toe. In early April, during evaluation before the second course of nivolumab for lung cancer, worsening swelling and pain of the right great toe were observed. Because of suspected disease progression, he was urgently hospitalized and later referred to our department.
At the initial visit, erythema, swelling, and warmth were noted around the distal nail fold of the right great toe (Fig. 1a). Three weeks later, a palpable nodule appeared on the lateral nail fold, accompanied by surface erosion, ulceration, and bleeding (Fig. 1b).





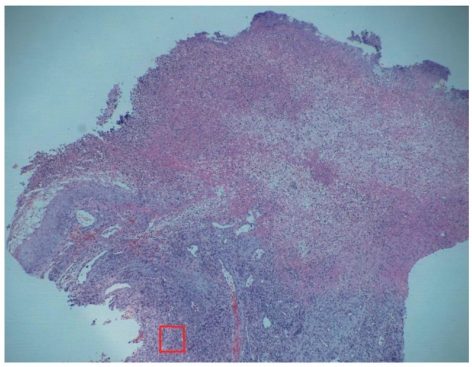
Case 12 – Laboratory and Histopathological Findings

Blood tests:
WBC 25,960/μL (Neutrophils 73%, Lymphocytes 14%, Monocytes 4%, Eosinophils 8%)
RBC 3.32 × 10^6/μL
Platelets 365 × 10^3/μL
BUN 11 mg/dL, Creatinine 0.73 mg/dL
AST 47 U/L, ALT 28 U/L
LDH 408 U/L, CK 71 U/L
Albumin 2.9 g/dL, Total protein 7.9 g/dL

CRP 5.52 mg/dL
SCC 119.3 ng/mL (reference <1.5)
CYFRA21-1 11.9 ng/mL (reference <2.8)

Histopathological findings:
A skin biopsy from the lateral nail fold revealed dense infiltration of inflammatory cells extending from the upper to mid dermis, with numerous atypical eosinophilic tumor cells forming sheets (Fig. 2a, b). Immunohistochemistry confirmed that tumor cells were positive for CK5 and p40 (Fig. 3a, b).

CT findings:
CT imaging of the right lower extremity demonstrated a 38-mm solid mass at the tip of the right great toe with osteolytic changes and continuity to the distal phalanx (Fig. 4a, b).



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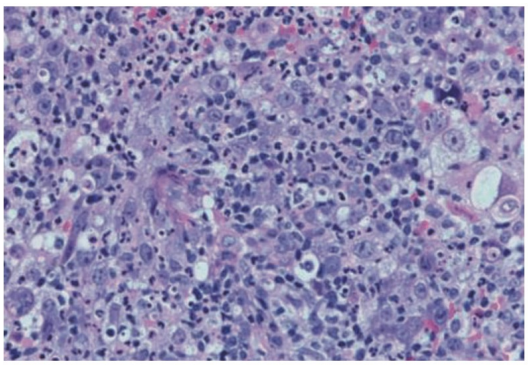

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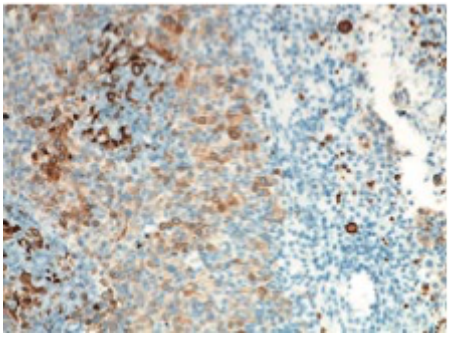
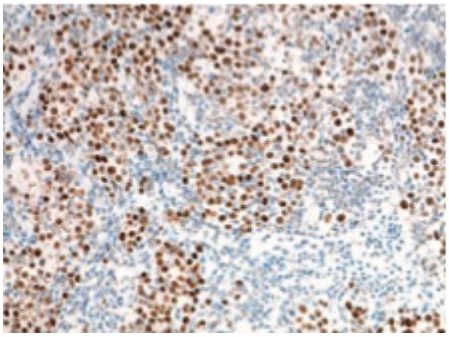
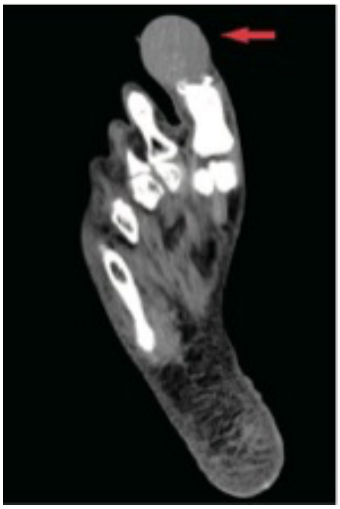
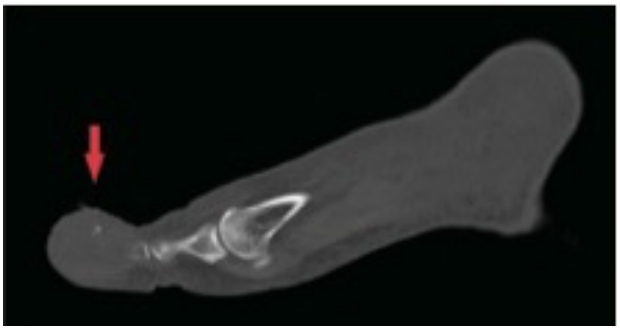






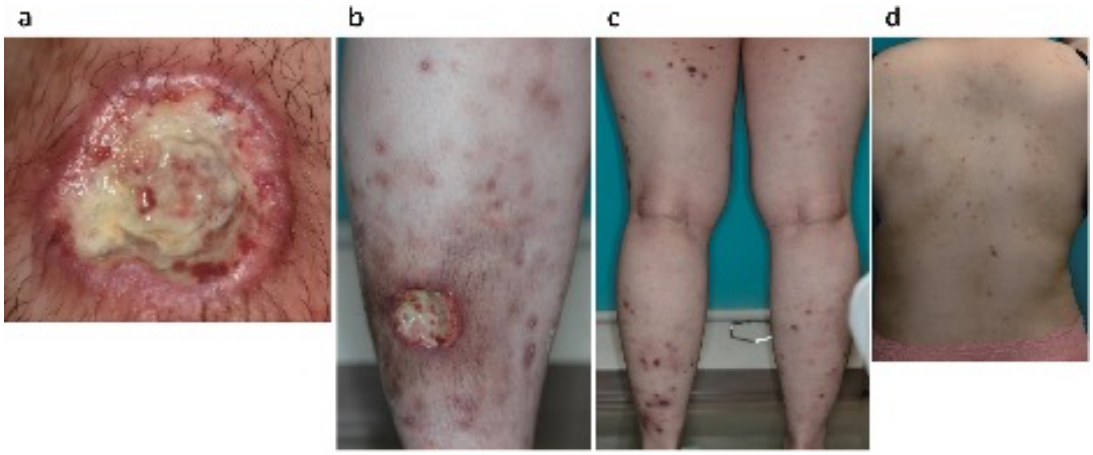


Case 13 – Basic Information and Clinical Findings

Patient: 30-year-old woman
Past history: Depression (treated with Years Flex O® combination tablet since February 2021)

History of present illness:
Since elementary school, she had recurrent crops of pruritic papules on the extremities that repeatedly appeared and regressed. Topical steroids were prescribed at a local clinic. Seven months before presentation, an ulcer appeared on the right lower leg at the site corresponding to previous erosion. Despite receiving topical and oral antibiotics and mupirocin ointment, the ulcer did not heal, and she was referred to our department.

Current findings:
A 3 cm × 3 cm deep cutaneous ulcer with violaceous undermined borders was present on the right lower leg. Crusted papulonecrotic lesions surrounded the ulcer, along with multiple old scars showing geometric, dark brown pigmentation caused by adhesive dressings (Fig. 1).



Case 13 – Laboratory and Histopathological Findings

Laboratory findings:
WBC 11.4 × 10^3/μL (Seg 74.6%, Ly 20.5%), Hb 12.4 g/dL, Plt 378 × 10^3/μL, BUN 10 mg/dL, Cr 0.74 mg/dL, AST 11 U/L, ALT 9 U/L, LDH 126 U/L, CRP 0.59 mg/dL, Na 138 mEq/L, K 4.2 mEq/L, IgE 1,632.6 IU/mL, sIL2R 431 U/mL.
RPR (−), TPHA (−), HBV antigen (−), HBs antibody (−), HCV antibody (−), HIV antibody (−).

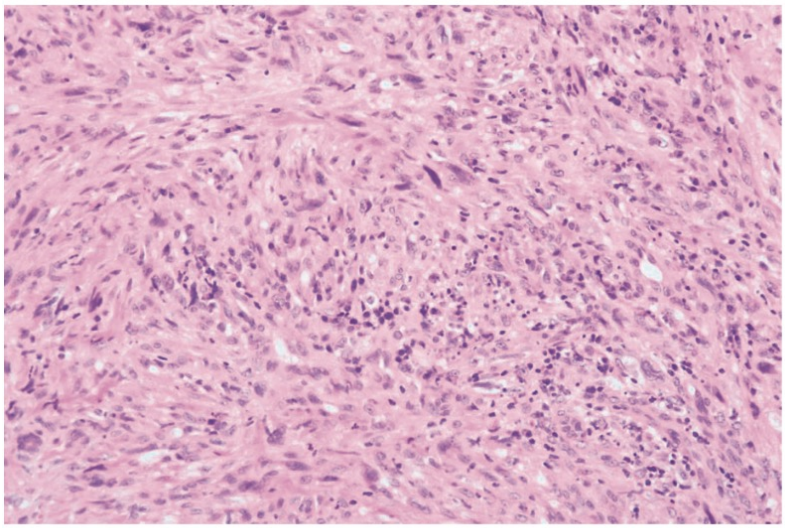
MRI findings:
MRI performed at admission showed that the ulcer extended to subcutaneous tissue with T1 low signal and T2 high signal in the surrounding soft tissues, suggesting inflammation.

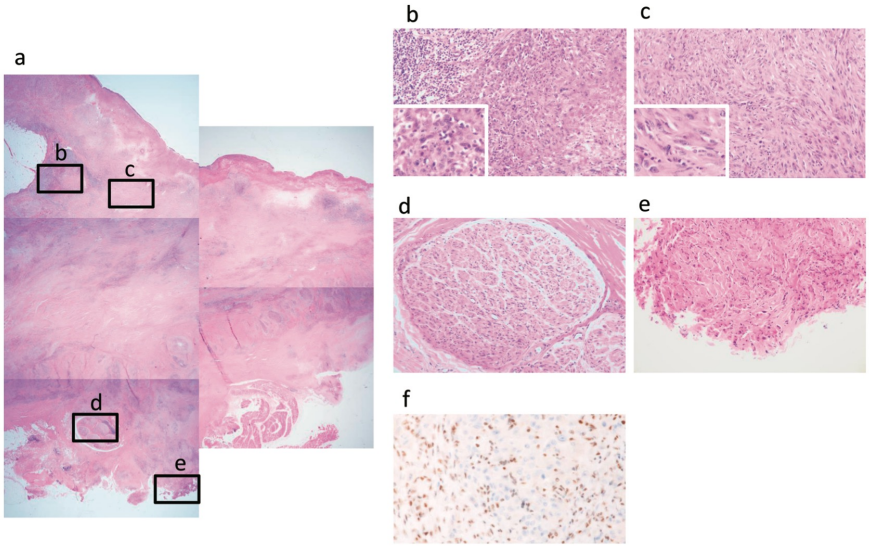
Histopathological findings of skin biopsy:
Dense infiltration of atypical neutrophils in the dermis surrounding the ulcer was observed. Foci of necrosis, leukocytoclastic vasculitis, and abscess formation were present (Fig. 2). No evidence of fungal or bacterial infection was found. CD3-positive lymphoid cells were observed only sparsely; CD34 and factor XIIIa were negative; S100 was negative, making malignancy unlikely. These findings supported a diagnosis of early-stage pyoderma gangrenosum.

Clinical course 1:
After two months of treatment, surgical debridement of the right inguinal lymph node was performed. No metastasis was detected, and the necrotic tissue was removed.

Findings from the wide excision specimen:
Extensive ulceration with granulation tissue and diffuse inflammatory infiltrates were seen (Fig. 3a–f). The atypical neutrophil-rich infiltration extended into the subcutaneous fat (Fig. 3b). No malignancy was present (Fig. 3c). The subcutaneous tissue displayed chronic inflammation but no abscess (Fig. 3d). Epidermal regeneration was confirmed at the ulcer edge (Fig. 3e). INI-1 expression was retained (Fig. 3f).

Metastatic lymph node evaluation:
Right inguinal lymph node biopsy revealed inflammatory changes without malignancy (Fig. 4a). INI-1 staining of the lymph node was negative in atypical myeloid cells (Fig. 4b).

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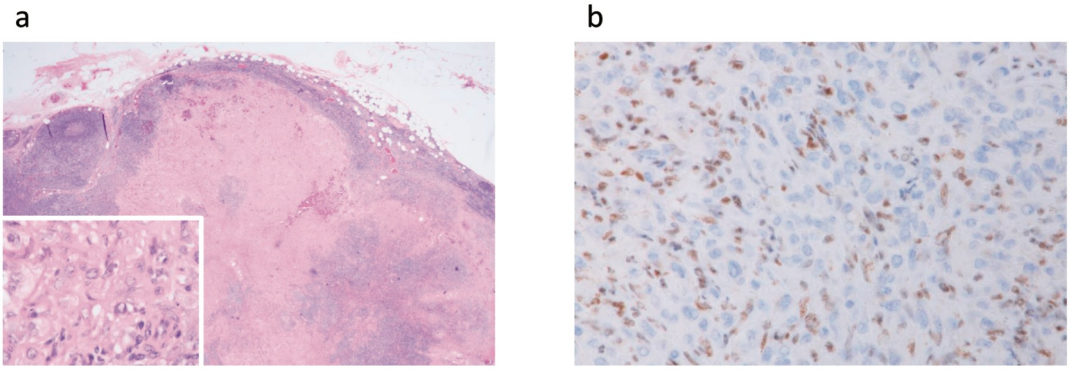
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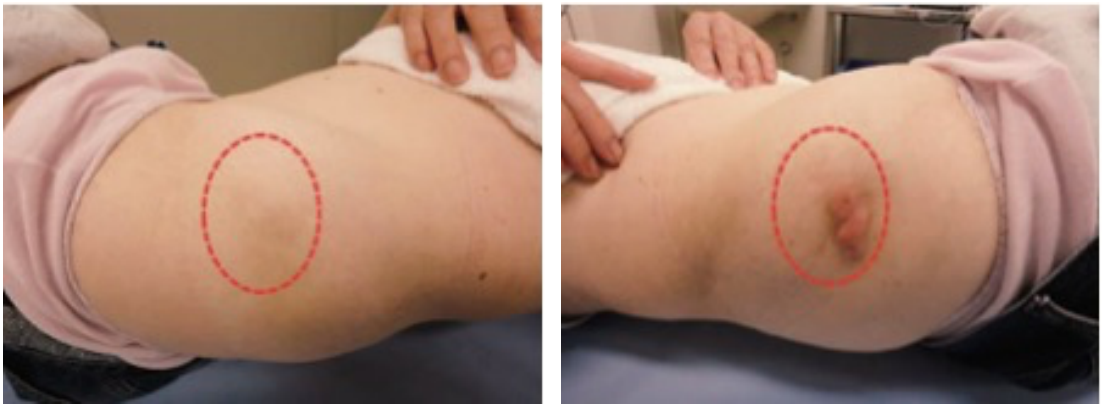
Case 14 – Basic Information and Clinical Findings

Patient: 77-year-old woman
Chief complaint: Subcutaneous tumors of the bilateral iliac regions

Family history: Unremarkable

History of present illness:
The patient noticed subcutaneous tumors in the bilateral iliac regions about three months before the initial visit. Because they gradually increased in size, she presented to our department.
Initial examination revealed a soft, elastic subcutaneous tumor on the left iliac region (Fig. 1a), and a 4 × 2 cm firm subcutaneous tumor with mild surface erythema and slight adhesion to the surrounding tissue on the right iliac region (Fig. 1b).

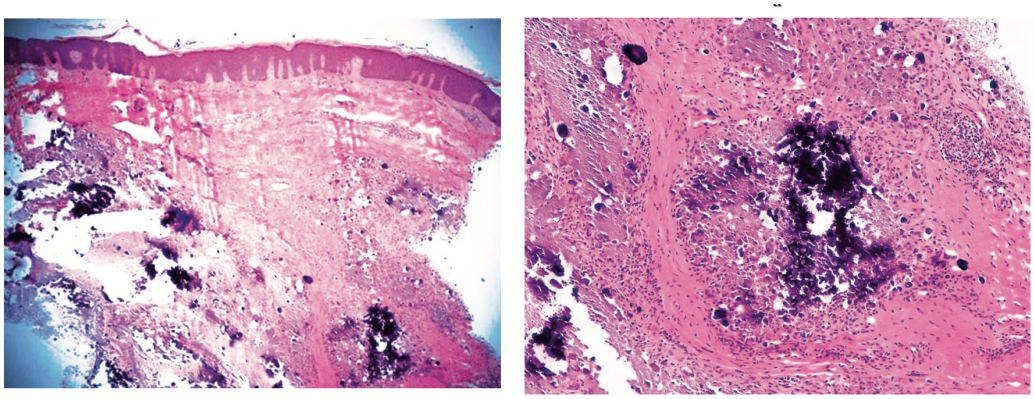


Case 14 – Laboratory and Histopathological Findings

Blood test results:
WBC 4,690/μL, Neut 64.8%, Mono 4.2%, Lymp 23.3%, Eos 5.0%, RBC 4.00 × 10^6/μL,
Hb 12.9 g/dL, Plt 256 × 10^3/μL, AST 18 U/L, ALT 15 U/L, LDH 186 U/L,
ALP 248 U/L, γ-GTP 13 U/L, CK 95 U/L, BUN 13 mg/dL, Cre 0.53 mg/dL, CRP 0.08 mg/dL,
Ca 9.4 mg/dL, IP 3.4 mg/dL (normal 2.7–4.6 mg/dL),
PTH intact ≤1.0 pmol/L (normal ≤1.1 pmol/L),
Whole-PTH 32.0 pg/mL (normal 8.3–38.7 pg/mL),
CEA 1.4 ng/mL (normal ≤5.0 ng/mL),

CA19-9 28.7 U/mL (normal ≤37.0 U/mL),
CA15-3 8.3 U/mL (normal ≤25.0 U/mL),
PIVKA-II 20.15 mAU/mL,
CH50 40.9 U/mL,
C3 102 mg/dL, C4 29.8 mg/dL,
Anti-dsDNA antibody <1.2 IU/mL,
Anti-Sm antibody negative,
Anti-Scl-70 antibody negative.

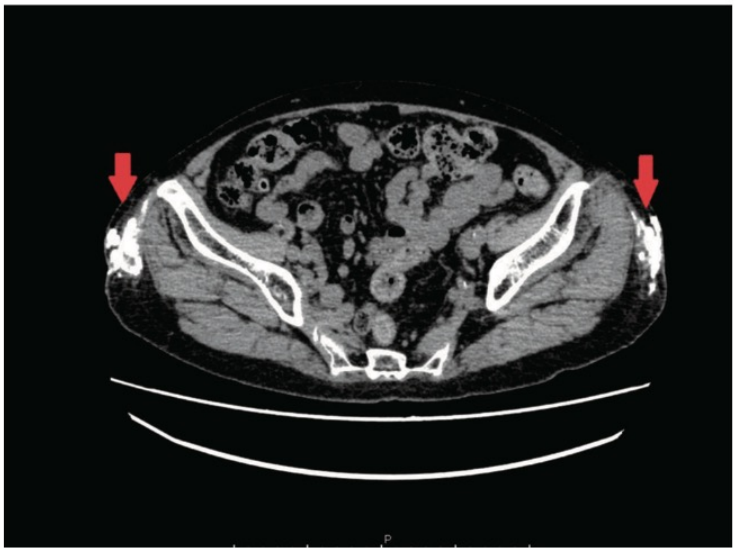
Histopathology of left iliac region biopsy:
Biopsy of the left iliac subcutaneous tumor revealed basophilic, calcified material with surrounding inflammatory cell infiltration. Histopathology suggested deposition of calcified material derived from degenerated fat tissue (Fig. 2a). Foreign-body giant cells were not detected. Mild lymphocytic infiltration surrounding the calcified deposits was observed (Fig. 2b).

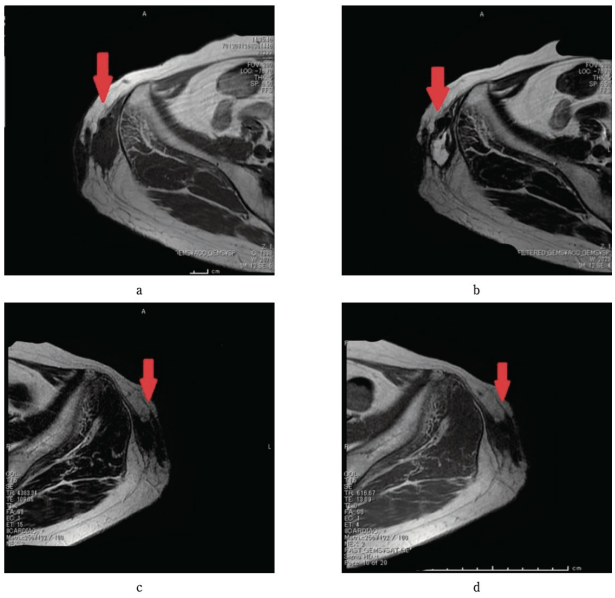


a b

MRI:
Pelvic MRI showed bilateral subcutaneous masses with low signal intensity on both T1- and T2-weighted images (Fig. 3). On the right side, partial high-signal areas were seen, suggesting internal heterogeneity.

CT:
Pelvic CT demonstrated calcification-dominant soft tissue densities within the subcutaneous fat layers lateral to the gluteal muscles bilaterally (Fig. 4).





Case 15 – Basic Information and Clinical Findings

Patient: 75-year-old woman
Chief complaint: Tumor of the chest wall

Past history:
Osteoporosis treated with oral alfacalcidol.

History of present illness:
Approximately 20 years earlier, she underwent excision of a chest wall tumor measuring about 2 cm at a local clinic, but the diagnosis was unknown. Two years later, the tumor recurred, but she left it untreated because it

caused no symptoms. About three months before presentation, the tumor rapidly enlarged with redness and warmth, prompting her to seek medical attention.

Current findings:
On the chest wall, a dome-shaped elastic-hard tumor measuring 7 cm in diameter and 2 cm in height was present. The overlying skin showed erythema and warmth. The tumor showed poor mobility relative to the chest wall and poor mobility relative to the overlying skin (Fig. 1). No cervical or axillary lymphadenopathy was detected.

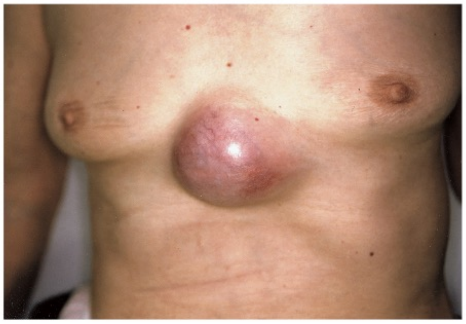


Fig. 1 Clinicl Appearance of the Tumor on the Middle Chest

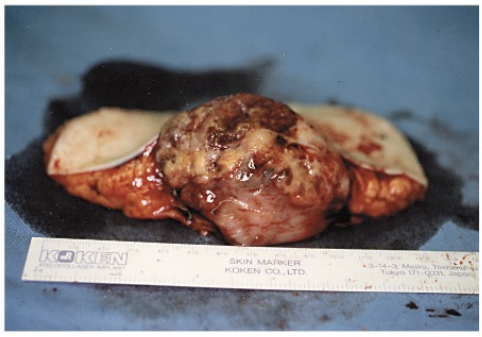


Fig. 2 The Cut Surface of the Resected Tumor
The Tumor had bleeding.

Case 15 – Laboratory and Histopathological Findings

Laboratory findings:
Hematologic and biochemical tests showed no abnormalities. CT revealed a well-demarcated subcutaneous chest wall mass. MRI showed a tumor extending from the lower chest to the abdominal muscles with partial fat signal loss. Gallium scintigraphy demonstrated no abnormal accumulation, making metastasis to other organs unlikely.

Intraoperative findings:
The tumor was relatively easily dissected from surrounding tissues. No nerve contiguous with the tumor was identified. Cut sections of the excised specimen showed a well-circumscribed yellowish-white solid tumor with partial hemorrhage (Fig. 2).

Histopathological findings:
The tumor showed proliferation of spindle-shaped to polygonal cells with nuclear atypia arranged in fascicles

within the dermis (Fig. 3). Immunohistochemistry showed positivity for S-100 protein (Fig. 4) and vimentin, and negativity for cytokeratin, α-smooth muscle actin, and EMA.

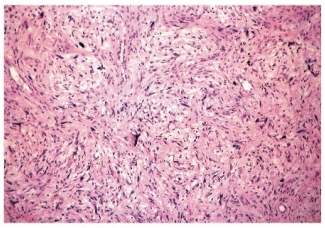


Fig. 3 Histological Findings

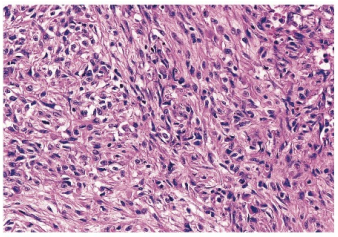


Fig. 3 Histological Findings of Metastatic Lymph Node

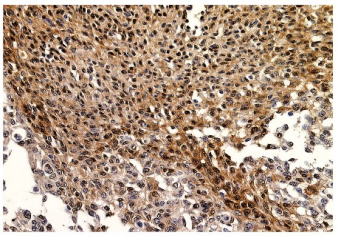


Fig. 4 Immunohistichemical Findings; s-100 Protein

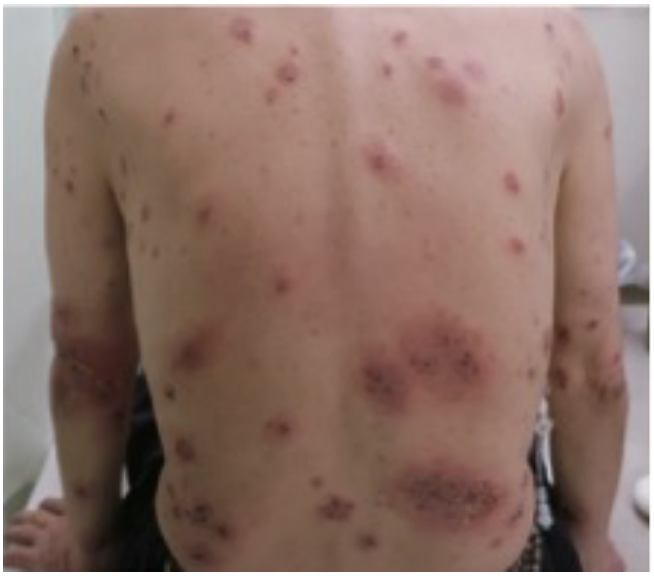
Case 16 – Basic Information and Clinical Findings

Patient: 67-year-old man
Chief complaint: Generalized erythema and blistering

Past history: Small cell lung carcinoma (under treatment)

History of present illness:
The patient had been treated with nivolumab for lung cancer for approximately two years and one month. Two months before presentation, erythema and tense blisters began to appear across the body. Because the symptoms did not improve, he was referred to our department for further evaluation and treatment.

Current findings:
Multiple widespread erythematous patches, erosions, and tense blisters were observed throughout the body. Many lesions showed serous exudation and surrounding erythema (Fig. 1).



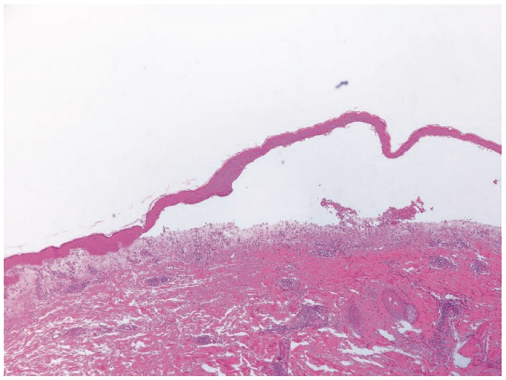
Case 16 – Laboratory and Histopathological Findings

Laboratory findings:
Anti-desmoglein-1 antibody <3.0, anti-desmoglein-3 antibody <3.0, anti-BP180 antibody 348 U/mL (elevated).

Histopathological findings:
A biopsy taken from a tense blister on the chest revealed a subepidermal blister. Numerous eosinophils and lymphocytes had infiltrated the blister cavity and upper dermis (Fig. 2a, b).

Immunofluorescence findings:

Direct immunofluorescence demonstrated linear deposition of IgG and C3 along the basement membrane zone (Fig. 3).



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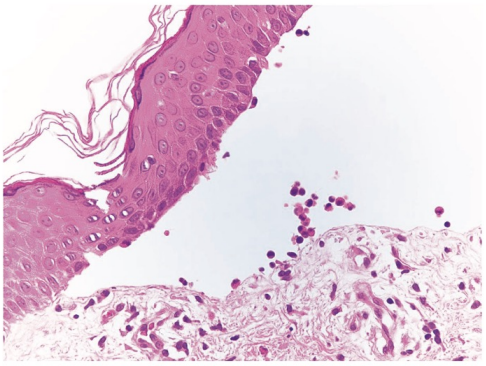

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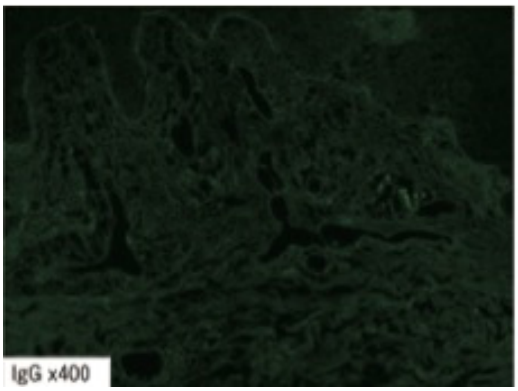
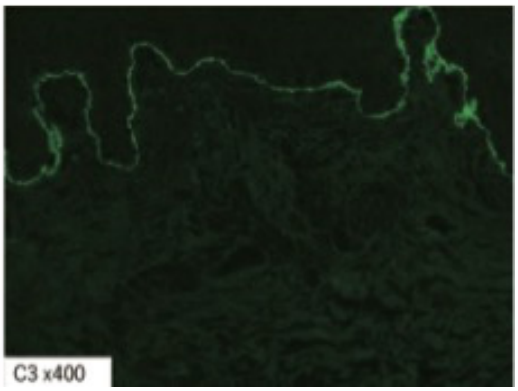




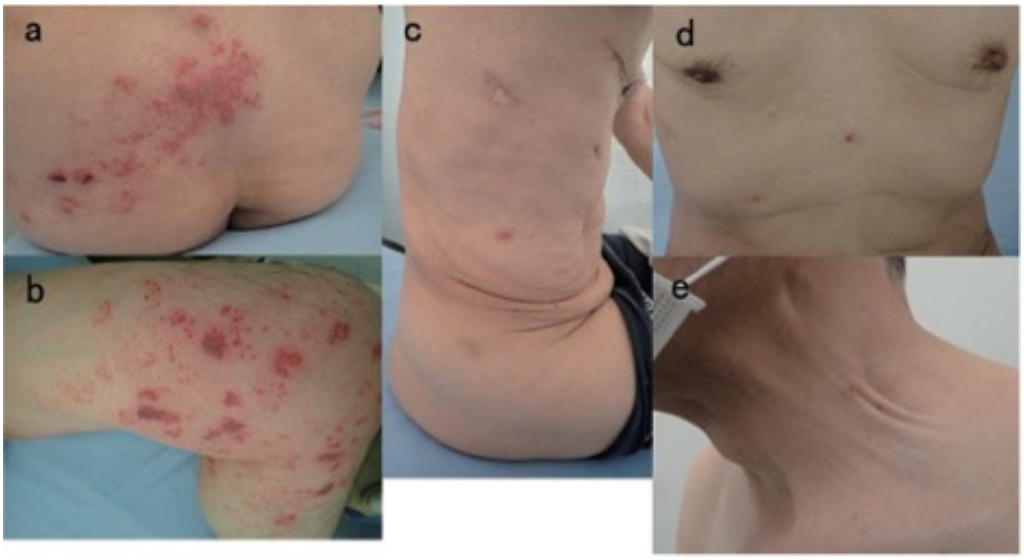
Case 17 – Basic Information and Clinical Findings

Patient: 70-year-old man
Chief complaint: Erythema and vesicles on the left thigh

Past history: Lung cancer (postoperative), atrial fibrillation, hyperthyroidism, left renal cancer
Family history: Unremarkable

History of present illness:
In December 20XX, erythematous lesions appeared on the left thigh and abdomen. He visited a local clinic and started treatment, but four days later he developed headache, nausea, and mild fever, leading to referral to our department for further evaluation.

Current findings:
Grouped small vesicles accompanied by pain and pruritus were present on the left sacral region, abdomen, and lower back (T10–L3 dermatomes), forming band-shaped reddish-brown patches. Similar vesicles were also observed on the head and trunk (Fig. 1a–e).



Case 17 – Laboratory and Additional Findings

Blood test results:
WBC 3,810/μL, Neut 60.9%, Eos 2.9%, Lymph 24.1%, RBC 4.28 × 10^6/μL, Hb 13.2 g/dL, Plt 177 × 10^3/μL, TP 7.2 g/dL, ALB 6.5 g/dL, AST 19 U/L, ALT 19 U/L, LDH 170 U/L, CRP 0.16 mg/dL, Cr 1.0 mg/dL.
VZV IgG 80.6 (+), VZV IgM 6.98 (+).

Neurological findings:
The patient was alert, with no signs of meningeal irritation. No focal neurological deficits were observed. Sensory testing revealed reduced pain and vibration sensation. Cranial CT and MRI showed no abnormalities.

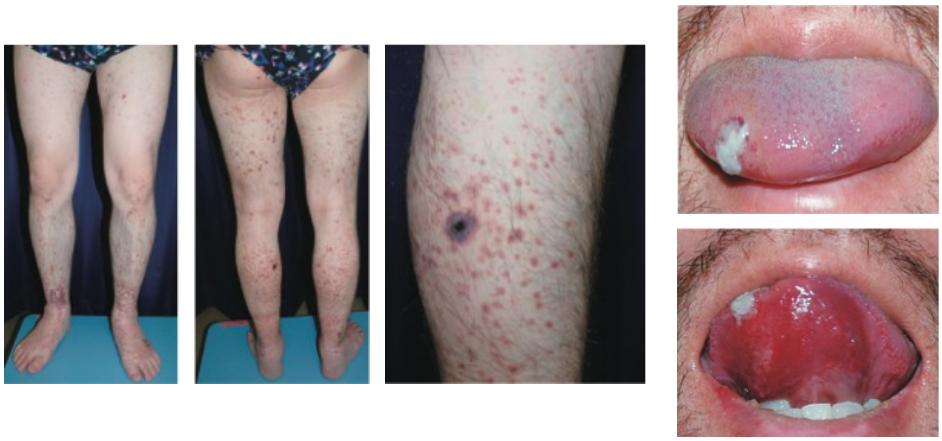
Cerebrospinal fluid (CSF) findings:
Appearance: clear and colorless
Protein 42.8 mg/dL, Glucose 58 mg/dL, Cell count 21/μL (0% neutrophils, 34% lymphocytes, 64% macrophages).
VZV IgG 3.98 (+), VZV IgM 0.49 (−).
PCR test detected VZV-DNA in CSF, confirming positivity.

Case 18 – Basic Information and Clinical Findings

Patient: 33-year-old man
Chief complaint: Purpura and leg pain

History of present illness:
Since December 2014, the patient had recurrent cold-like symptoms and visited a local physician. He was treated with antibiotics and tranexamic acid, with partial improvement, but respiratory discomfort, sore throat, and cough persisted.
Three days before the first dermatology visit, purpura appeared on the legs and back. Two days before the visit, the purpura expanded and leg pain worsened, prompting referral to our department in January 2015.

Current findings:
Body temperature was 37.8°C with mild right shoulder tenderness but no gastrointestinal symptoms.
Palpable purpura were present from the lower legs to the lumbar region and extending to the upper limbs and fingers. Some lesions on the lower legs and feet were necrotic. Lower-leg pain was also noted (Fig. 1a–c).



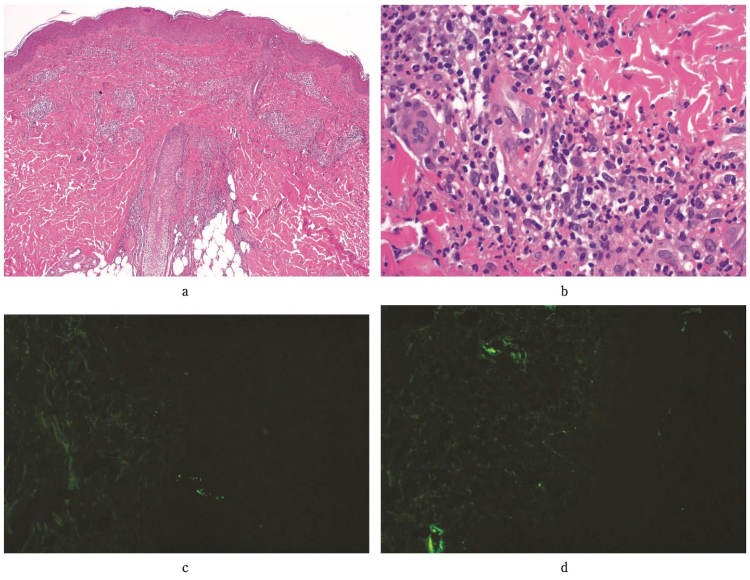
Case 18 – Laboratory and Histopathological Findings

Laboratory findings:
WBC 10,530/μL (Neut 72.9%, Lym 18.6%, Mo 6.5%, Eos 1.4%), RBC 3.41 × 10^6/μL, Hb 11.0 g/dL, Plt 281 × 10^3/μL.
AST 24 U/L, ALT 48 U/L, γ-GTP 31 IU/L, LDH 294 U/L.
BUN 20 mg/dL, Cr 0.64 mg/dL, CRP 1.30 mg/dL.

PT 91%, PT-INR 1.06, APTT 26.5 sec, Fibrinogen 319 mg/dL, D-dimer 5.5 μg/mL, FDP 12.0 μg/mL (>10).
IgG 1,073 mg/dL, IgA 197 mg/dL, IgM 30 mg/dL.
C3 127 mg/dL, C4 38 mg/dL, CH50 46.7 U/mL.
P-ANCA <1.0, C-ANCA <1.0, ANF <40.

Urinalysis:
Glucose (−), protein (+/−), occult blood (−), urobilinogen (−), WBC 1–4/HPF, RBC 1–4/HPF, epithelial cells 1–4/HPF, bacteria (−), casts (−).

Histopathological findings of skin biopsy:
Biopsy from the purpuric lesion on the right thigh revealed leukocytoclastic vasculitis.
H&E staining showed dense infiltration of neutrophils and nuclear dust around small vessels in the dermis and subcutis, along with fibrinoid necrosis of vessel walls (Fig. 2a, b).
Direct immunofluorescence demonstrated granular deposition of IgA and C3 around dermal vessel walls (Fig. 2c, d).

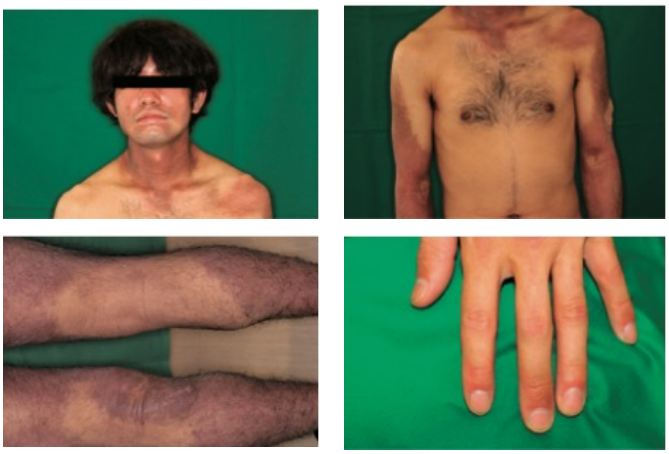


Case 19 – Basic Information and Clinical Findings

Patient: 25-year-old man

History of present illness:
The patient had been treated with topical difluprednate ointment and betamethasone valerate ointment.
In early March of year X, erythema on the face worsened. Erythematous eruptions subsequently appeared on the extremities, and by early April he developed weakness when lifting objects and difficulty making a fist with both hands.
A nearby dermatologist suspected atopic dermatitis and initiated treatment, but symptoms persisted. Due to continued poor condition, he was referred to our department.

Current findings:
Linear erythema extending from the face to the neck was observed (Fig. 1a).
The neck showed V-neck–shaped erythema (Fig. 1a).
There was no heliotrope rash around the eyes.
No eruptions were seen on the trunk, but both upper extremities showed scratch dermatitis–like linear excoriated erythema (Fig. 1b).
Erythema with scale was seen on the extensor forearms, but no eruptions were noted on the knees (Fig. 1c).
On the fingers, erythema with fissuring was found at the MP joints.
Erythema was also seen around the posterior auricular region (Fig. 1d).
No vesicles were observed.
Manual muscle testing revealed 4− in the deltoid and iliopsoas.



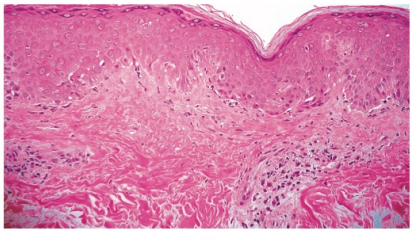
Case 19 – Laboratory and Histopathological Findings

Laboratory findings:
Blood tests showed: WBC 7,000/μL (11.0% eosinophils), CRP 0.3 mg/dL, ESR 20 mm/h, suggesting mild eosinophilia.
AST 71 IU/L, ALT 61 IU/L, LDH 665 IU/L, CK 468 IU/L, aldolase 13.7 IU/L, and myoglobin 171.1 ng/mL were elevated.
Anti–Jo-1 antibody was negative, with a titer <1:40. Anti–TIF1-γ antibody was positive at index 94.
Other myositis-associated antibodies (Mi-2, ARS, MDA5) were negative.
Brain MRI was unremarkable. Needle EMG revealed myopathic changes in the right deltoid, right triceps, right iliopsoas, and right anterior tibialis muscles, confirming myositis.

Histopathological findings:
A biopsy of the erythematous lesion on the left upper arm and a concurrent biopsy of the left quadriceps muscle were performed.
Skin biopsy revealed epidermal atrophy with liquefaction degeneration of the basal layer, and dermal edema with mucin deposition. Sparse necrotic keratinocytes were present.
Dermal perivascular lymphocytic infiltrates with mild separation of collagen bundles were also observed (Fig. 2a).

Alcian blue staining (pH 2.5) highlighted mucin deposition in the dermis (Fig. 2b).

Muscle biopsy showed the presence of polygonal fibers, with sparse endomysial lymphocytic infiltrate but no findings suggestive of muscle fiber necrosis or perifascicular atrophy (Fig. 2c).



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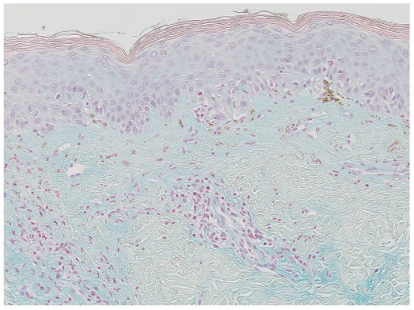

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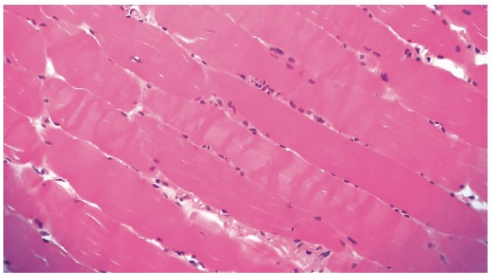

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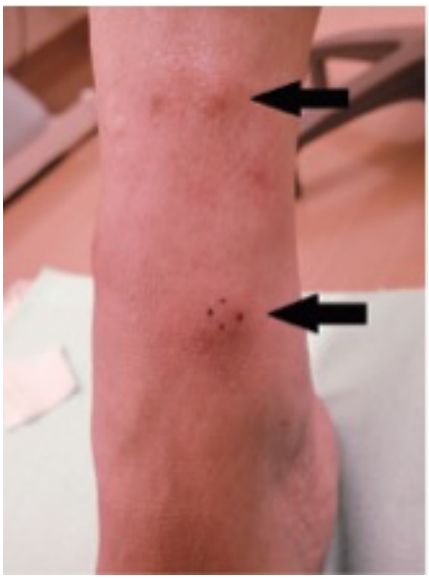
Case 20 – Basic Information and Clinical Findings

Patient: 77-year-old woman
Chief complaint: Painful erythema of the right lower leg
Family history: Unremarkable
Past medical history: Colon cancer (surgery 10 years ago), thyroid cancer (postoperative, 12 years ago), aortic valve replacement, uterine fibroid surgery, sclerosing adenosis, renal dysfunction

History of present illness:
One month before presentation, painful infiltrated erythema appeared on the right lower leg. There were no preceding infectious symptoms or external injury. Symptoms did not improve, and she was referred to our department.

Current findings:
Painful erythema with induration was observed on the extensor surface of the right lower leg, forming two nodular lesions up to the mid-lower leg (Fig. 1).



Case 20 – Laboratory, Histopathological, and Imaging Findings

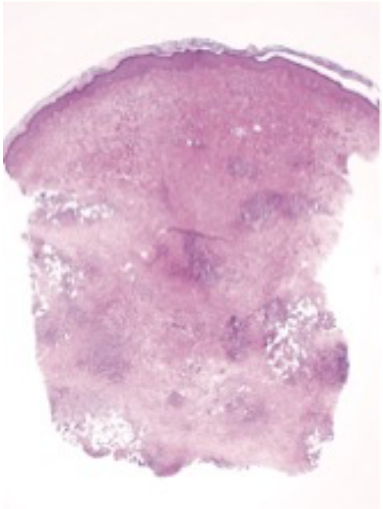
Laboratory findings:
WBC 7,800/μL (Seg 74.2%, Lym 19.2%, Mono 5.0%, Eos 1.3%, Baso 0.3%),
RBC 4.30 × 10^6/μL, Hb 11.4 g/dL, Plt 149 × 10^3/μL,
AST 17 U/L, ALT 9 U/L, LD 181 U/L, γ-GTP 23 U/L, T-Bil 0.63 U/L, Alb 3.7 g/dL,
Na 142 mEq/L, Cl 103 mEq/L, K 3.9 mEq/L,

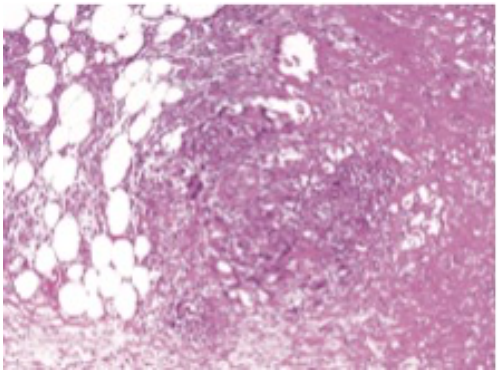
BUN 19.5 mg/dL, Cr 0.79 mg/dL, CRP 3.05 mg/dL.

Histopathological findings:
The epidermis showed no remarkable changes. Dense inflammatory infiltrates were present around deep dermal blood vessels and within adipose tissue.
The infiltrate consisted mainly of lymphocytes, histiocytes, neutrophils, and multinucleated giant cells, forming granulomatous nodules (Fig. 3a, b).
No caseous necrosis was seen, and there was no clear evidence of vasculitis. Ziehl–Neelsen staining was negative.

Imaging findings:
Chest and pelvic CT revealed no active pulmonary findings but did show calcified nodules consistent with old granulomatous disease.

Additional information:
Medical history revealed pulmonary tuberculosis treated 27 years prior. T-SPOT was positive, and tuberculin skin test was also positive.





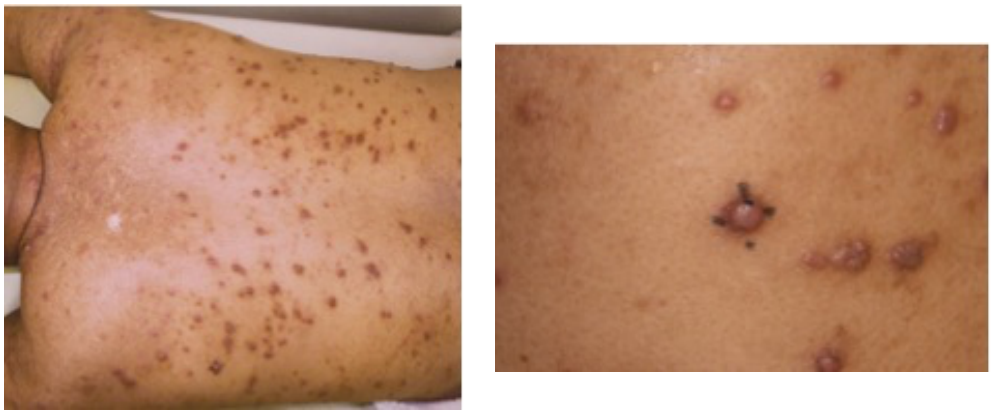
Case 21 – Basic Information and Clinical Findings

Patient: 48-year-old man
Chief complaint: Asymptomatic reddish papules scattered over the trunk and extremities

History of present illness:
Since childhood, he had scattered papules consistent with prurigo, which later stabilized without treatment.

At age 30, he developed non-pruritic reddish papules on the trunk and extremities and visited a dermatologist. He was diagnosed with atopic dermatitis and treated with betamethasone valerate propionate ointment and betamethasone butyrate propionate ointment. Despite continuous treatment, the eruptions repeatedly improved and recurred, and he sought further evaluation.

Current findings:
Multiple 6–10 mm reddish papules were scattered primarily on the trunk (Fig. 1).
No lymphadenopathy was noted.



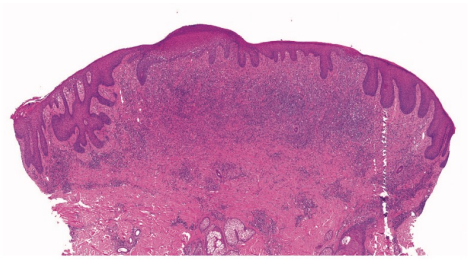
Case 21 – Laboratory and Histopathological Findings

Laboratory findings:
WBC 8,000/μL (Eos 7.0%), Hb 15.3 g/dL, Plt 204 × 10^3/μL, AST 13 U/L, ALT 11 U/L, LDH 197 IU/L, T-Bil 0.8 mg/dL, TP 6.9 g/dL, Alb 3.6 g/dL (reference 3.9–4.9 g/dL), BUN 12.6 mg/dL, Cre 0.80 mg/dL, IgG 1,401 mg/dL, IgA 280 mg/dL, IgM 57 mg/dL, markedly elevated IgE 10,033 IU/mL (ref. <249.9 IU/mL), IgG4 185 mg/dL (reference 11–121 mg/dL), TARC 1,702 pg/mL (reference <450 pg/mL), κ/λ ratio 1.44, urinalysis normal; urine Bence–Jones protein negative; anti-nuclear antibody <1:40.

Histopathological findings:
Skin biopsy showed mild epidermal acanthosis and dense superficial perivascular and interstitial infiltrates composed mainly of lymphocytes. No distinct eosinophilic infiltration or flame figures were observed. Rare neutrophils and histiocytes were present, and atypia was not identified (Fig. 2).

Immunohistochemistry:
CD8- and CD20-positive cells were fewer than CD4-positive lymphocytes (Fig. 3).
The κ/λ ratio (1:2) showed no evidence of light-chain restriction (Fig. 4).

Among IgG-positive cells, 40–60% were IgG4-positive, with approximately 40 IgG4-positive plasma cells per HPF (Fig. 5).



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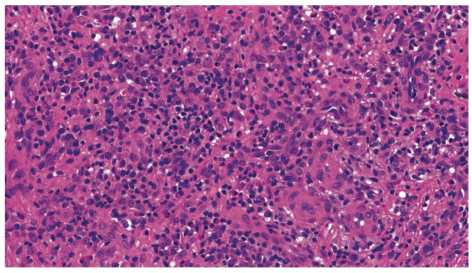

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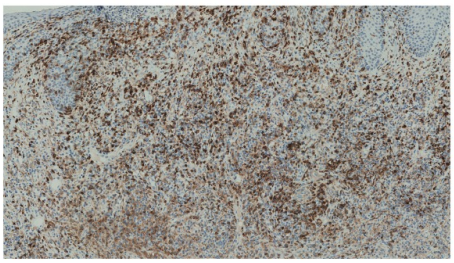

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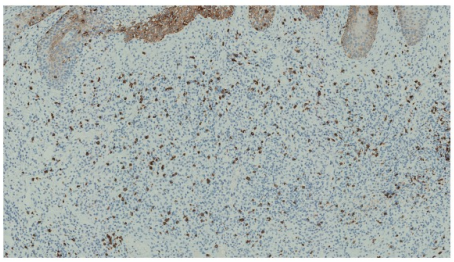

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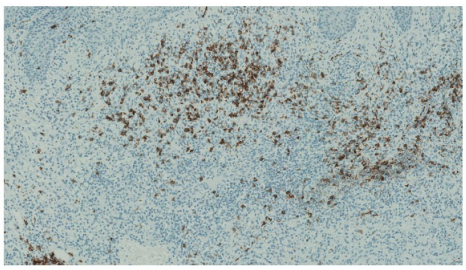

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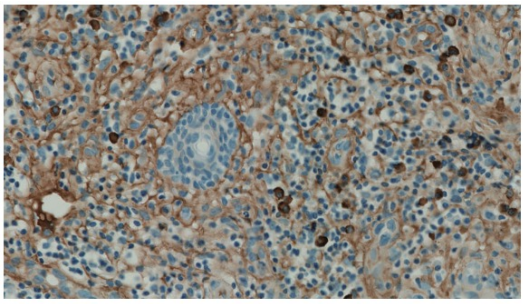

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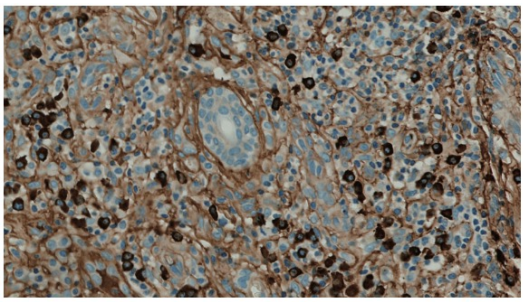

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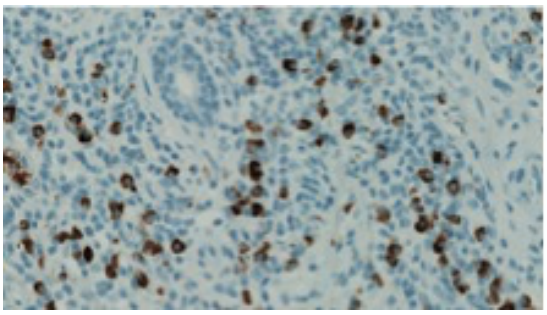
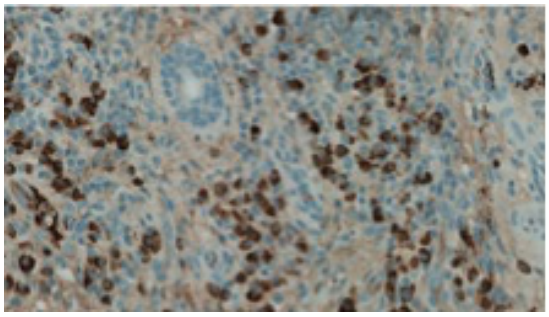


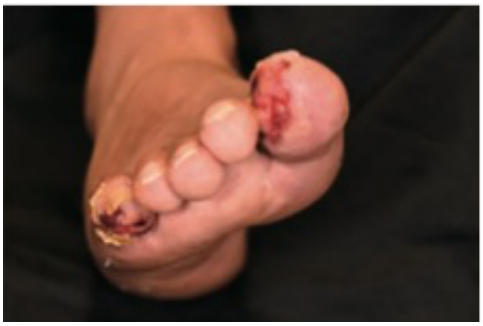


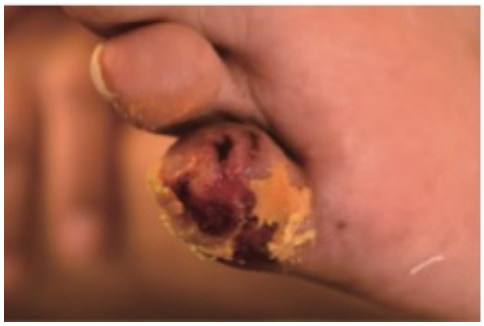
Case 22 – Basic Information and Clinical Findings

Patient: 48-year-old man
Chief complaint: Painful purpuric skin lesions on the right lower extremity
Lifestyle history: Smoked 40 cigarettes per day since age 20

History of present illness:
Around February of year X, the patient noticed coldness and pain in the right toes.
By July of year X, rest pain developed, and by September of year X, skin ulcers appeared on the right first toe.
Topical ointments were prescribed but were ineffective.
Because walking became increasingly difficult, he was referred to our department in April of the following year for further evaluation.

Current findings:
Necrotic ulcers with black eschar were present on the right first and fifth toes, accompanied by purpuric erythema.
Marked cold sensation was noted in the right foot.
Retiform purpura was observed from the dorsum to the plantar surface of the foot (Fig. 1a, b).
No ulcerative or purpuric lesions were noted on the fingers or upper extremities.
Severe periodontal disease associated with long-term smoking was also observed.

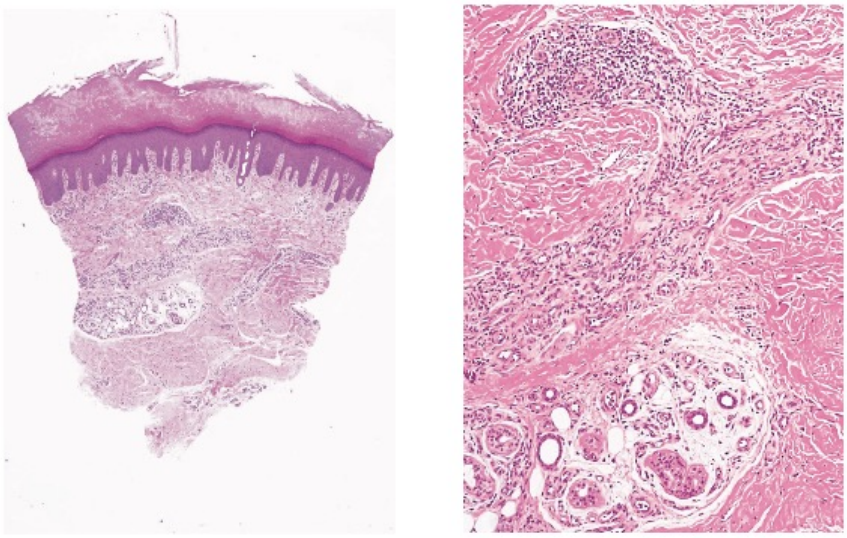




Case 22 – Laboratory and Histopathological Findings

Histopathological findings:
A biopsy of the purpuric erythematous lesion on the right dorsum of the foot revealed dense perivascular lymphocytic infiltration extending from the superficial to the deep dermis.

No definite fibrinoid necrosis of the vessel walls was observed (Fig. 2a, b).



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Laboratory findings:

Complete blood count:
WBC 6,600/μL (Neut 43.1%, Lymph 35.5%, Mono 9.4%, Eos 11.6%),
RBC 4.61 × 10^6/μL, Hb 14.4 g/dL, Plt 356 × 10^3/μL

Biochemical tests:
AST 11 U/L, ALT 8 U/L, ALP 255 U/L, BUN 26 mg/dL, Cr 0.78 mg/dL, CRP 2.89 mg/dL, Alb 3.8 g/dL, Na 143 mEq/L, K 4.1 mEq/L, PT-INR 1.08

Coagulation tests:
APTT 33 sec, D-dimer 1.19 μg/mL, FDP 3.6 μg/mL, fibrinogen 489 mg/dL,
Protein C activity 97%, Protein S

Vascular examinations:

1) Lower extremity arterial ultrasound:
Poor flow in bilateral lower extremities, indicating occlusive lesions.

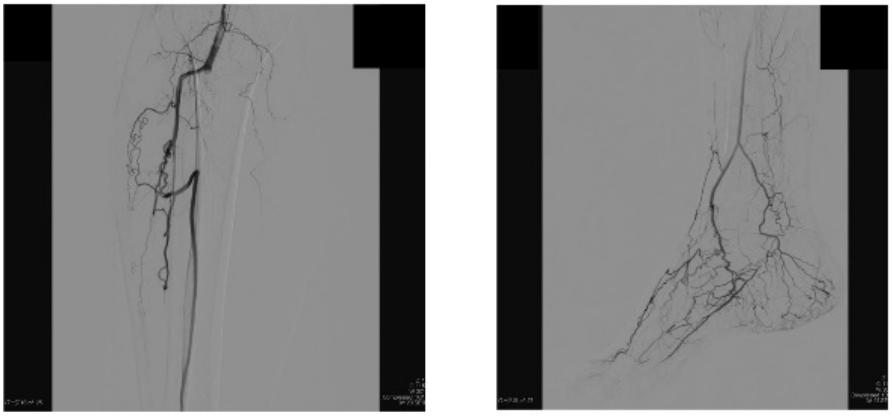
2) ABI:
Right 0.94, Left 1.08

3) Upper extremity arterial ultrasound:

No significant stenosis in bilateral brachial arteries; normal waveforms.

7) Chest–abdominal CT:
Severe atherosclerotic changes in thoracic and abdominal aorta.

8) Lower extremity angiography:
Right superficial femoral artery showed long-segment occlusion with extensive collateral formation.
Left superficial femoral artery also showed long-segment occlusion.
In the right lower extremity, blood flow to the foot was supplied only via collateral vessels throughout the calf region (Fig. 3a, b).



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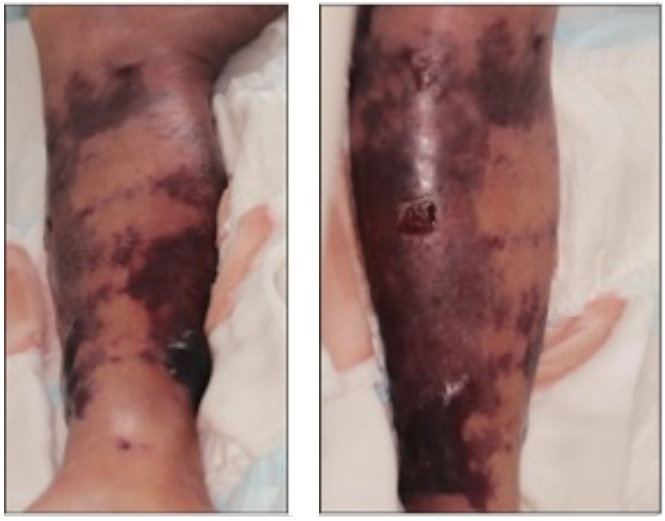
Case 23 – Basic Information and Clinical Findings

Patient: 90-year-old woman
Chief complaint: Right thigh pain and difficulty walking

History of present illness:
Seven days before presentation, bilateral lower-leg edema developed. She first visited a nearby internal medicine clinic the day before admission, where worsening chronic heart failure was suspected. Because of severe right thigh pain and difficulty walking, she was transferred emergently to our hospital and admitted to the cardiovascular department. She was then referred to our department for suspected cellulitis.
On examination, the right thigh showed purplish to red discoloration with increased warmth, raising concern for necrotizing fasciitis.
Initial vital signs: temperature 35.3°C, blood pressure 63/45 mmHg, SpO_2 unmeasurable, pulse 85/min, respiratory rate 23/min.

Current findings:
Marked swelling of both lower legs; the right thigh showed diffuse erythema with hemorrhagic blisters. Tenderness was noted over the thigh. Petechial to ecchymotic eruptions were observed over the right thigh and lower leg. Serous fluid drainage was present from the right lower-leg lesion (Fig. 1a, b).

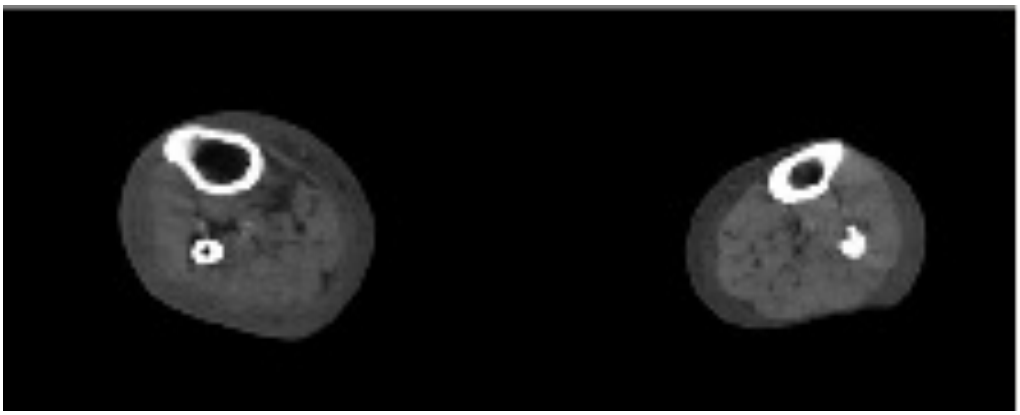


Case 23 – Laboratory and Imaging Findings

Laboratory findings:
WBC 5,300/μL (Neu 87.5%), Lym 7.6%, Mono 4.7%, Eos 0.0%, Baso 0.2%

RBC 3.91 × 10^6/μL, Hb 9.5 g/dL, Plt 22.2 × 10^3/μL
PT-INR 1.22, APTT 42.0 sec
Alb 2.1 g/dL, AST 36 U/L, ALT 36 U/L, LD 229 U/L, CK 219 U/L
Cre 0.9 mg/dL, BUN 32 mg/dL, CRP 4.12 mg/dL

Imaging findings:
Lower-limb CT showed high-density areas extending from the right knee to the ankle within the subcutaneous and muscle layers, but **no obvious gas formation was observed** (Fig. 2).

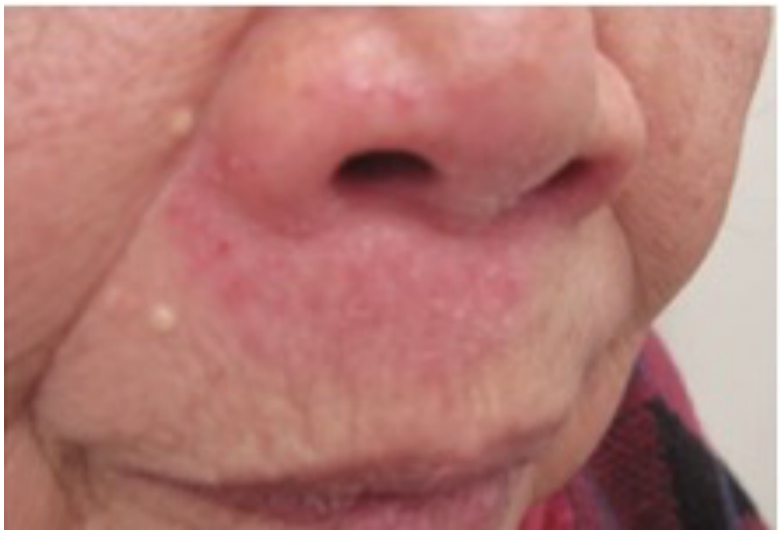


Case 24 – Basic Information and Clinical Findings

Patient: 82-year-old woman
Chief complaint: Erythema of the philtrum
Lifestyle history: Pet ownership (two cats)

History of present illness:
One month before presentation, erythema appeared around the right nasal ala and philtrum.
She visited a nearby internal medicine clinic and was treated with oxytetracycline ointment, followed by a switch to bepotastine besilate cream; however, after two weeks of use,
the eruption worsened, prompting referral to our department.

Current findings:
From the right nasal ala to the nasal vestibule and across the philtrum to the left nasal vestibule, a circular erythematous lesion with scaling was observed, with small pustules at the margin (Fig. 1a).



Case 24 – Laboratory and Histopathological Findings

Direct microscopy (KOH):
Scraping from the scaly margin demonstrated fungal hyphae consistent with dermatophytes.

Fungal culture findings:
Scales collected from the lesion were cultured on Mycosel agar at room temperature,
producing white powdery colonies that enlarged over two weeks to cover the entire agar surface.
The surface formed a fan-shaped pattern with short white peripheral filaments;

the central area showed powdery texture.
The surface coloration was uniformly pale yellow, and the reverse side was also pale yellow.

Direct microscopy of cultured specimen (Lactophenol Cotton Blue staining):
Microscopy of colony scrapings on day 20 revealed numerous macroconidia with thin cell walls and 5–6 internal septa.

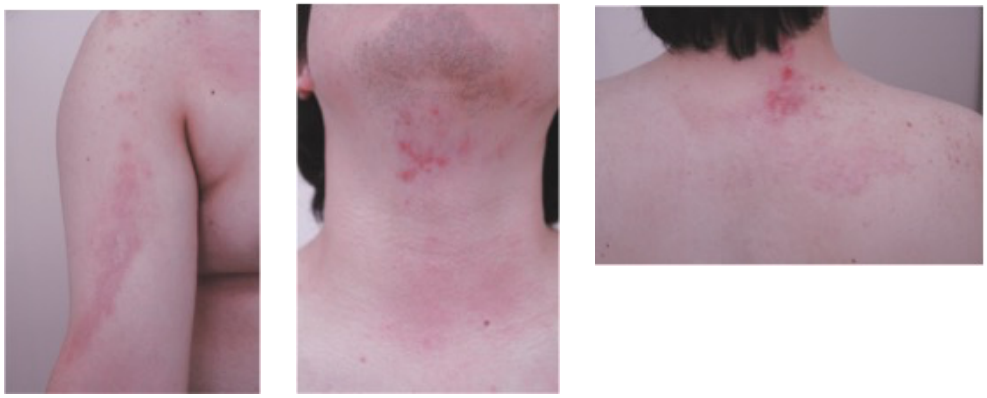
Molecular identification:
Sequencing of the ITS region of the isolate (KMU10134), performed at Kanazawa Medical University Department of Dermatology, demonstrated 100% identity with Nannizzia gypsea (reference strain CBS 258.61; Accession number NR_131271).

Case 25 – Basic Information and Clinical Findings

Patient: 20-year-old man
Past history / Family history: Unremarkable

History of present illness:
Approximately one year before the first visit, the patient noticed erythematous plaques on the neck and upper arm without pruritus. He was referred to our department in July 2013 for further evaluation. There was no history of trauma or prior cutaneous disease at the site of onset.

Current findings:
Linear erythematous plaques extended from the anterior neck to the right upper arm, following the Blaschko lines.
On the upper arm, the plaques showed a linear distribution with central and peripheral areas of whitish induration and atrophic changes (Fig. 1a–c).
No tenderness or pigmentary changes were observed.

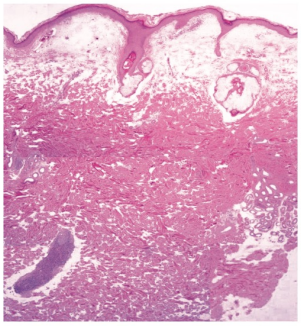


Case 25 – Laboratory and Histopathological Findings

Initial laboratory findings:
Routine hematological and biochemical tests were within normal limits. Autoantibodies, including ANA, were negative.

Histopathological findings (biopsy from right upper arm):
Marked epidermal atrophy with loss of rete ridges and compact hyperkeratosis were observed (Fig. 2a).

The upper dermis showed mild lymphocytic infiltration around adnexal structures and superficial blood vessels (Fig. 2b).
The lower dermis demonstrated increased collagen fiber density with thickened bundles and sparse lymphocyte infiltration (Fig. 2c).
These findings were consistent with a diagnosis of linear morphea.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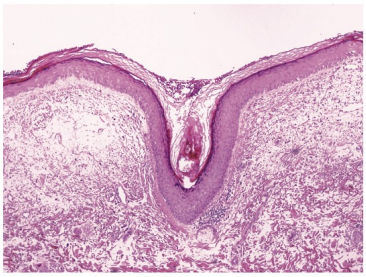
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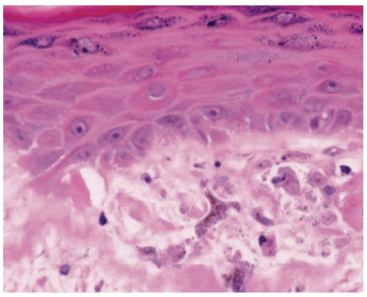
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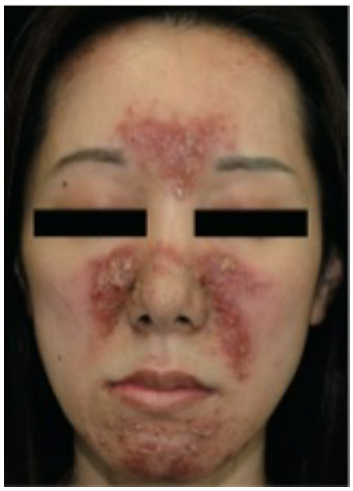
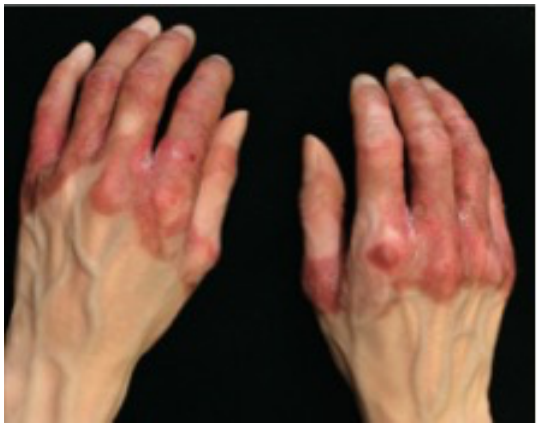
Case 26 – Basic Information and Clinical Findings

Patient: 44-year-old woman

History of present illness:
Three years prior to presentation, the patient began experiencing recurrent duodenal ulcers and subsequently developed gastric outlet obstruction due to scarring, requiring continued treatment at another hospital. Over the past few months, she developed worsening anorexia and general malaise. Two months before presentation, erythematous eruptions appeared on both hands. A dermatologist prescribed clobetasol propionate ointment and petrolatum-based moisturizer, but the eruptions spread and worsened, involving the dorsum of both hands and forearms. Ten days before her visit, erythema and pustules appeared on the face and auricles. Allergic contact dermatitis or fixed drug eruption was suspected, and a patch test panel (S) was performed by the previous clinic, but all results were negative. She was referred to our department for diagnostic evaluation.

Current findings:
Erythematous plaques with pustules were present on the forehead, cheeks, and chin. The bilateral auricles showed marked erythema with pustules. On the dorsum of both hands, erythema with pustules and scaling extended from the metacarpophalangeal joints to the forearms with well-demarcated dark-red margins. On the abdomen, scattered erythema and pustules were noted (Fig. 1a, b).



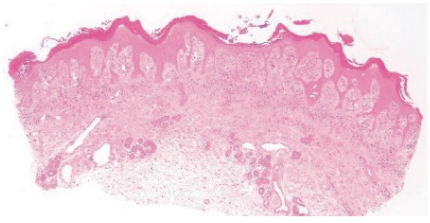


Case 26 – Laboratory and Histopathological Findings

Laboratory findings:
WBC 6,240/μL (Seg 69.7%, Lym 24.7%, Mono 5.0%, Eos 0.3%),
RBC 3.08×10^6/μL, Hb 10.8 g/dL, Plt 355×10^3/μL

AST 19 U/L, ALT 12 U/L, BUN 5 mg/dL, Cre 0.42 mg/dL
TP 8.7 g/dL, Alb 3.9 g/dL, CRP 0.05 mg/dL
Na 144 mmol/L, K 4.1 mmol/L, Cl 104 mmol/L
Zinc 94.3 μg/dL (ref 80–130), Folate 3.7 ng/mL (ref ≥4.0),
Vitamin B1 42 ng/mL (ref 24–66), Vitamin B2 108 ng/mL (ref 66–111),
Vitamin B12 1,840 pg/mL, Vitamin C 11.1 μg/mL (ref 5.5–16.8),
Fasting glucose 95 mg/dL, Gastrin 129 pg/mL (ref 0–200),
Tryptophan 41.0 nmol/mL (ref 37.0–74.9), Nicotinamide 3.6 μg/mL (ref 4.7–7.9).

Histopathological findings:
Biopsy of the skin demonstrated parakeratosis with neutrophil microabscesses, spongiosis, and marked acanthosis. In the superficial dermis, perivascular infiltration of lymphocytes and neutrophils was observed (Fig. 2a).
In some areas, intraepidermal neutrophilic microabscesses and vacuolar degeneration of the basal layer were seen, along with dermal edema and inflammatory infiltrates (Fig. 2b, c).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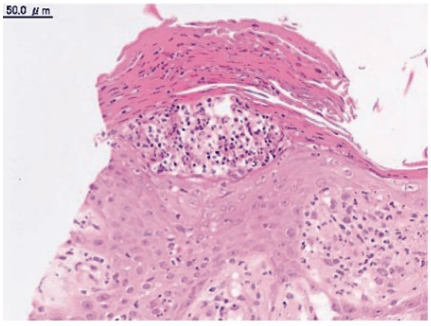

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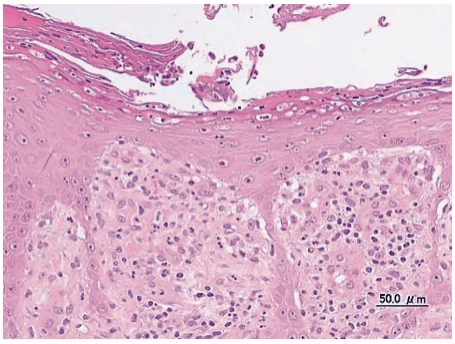

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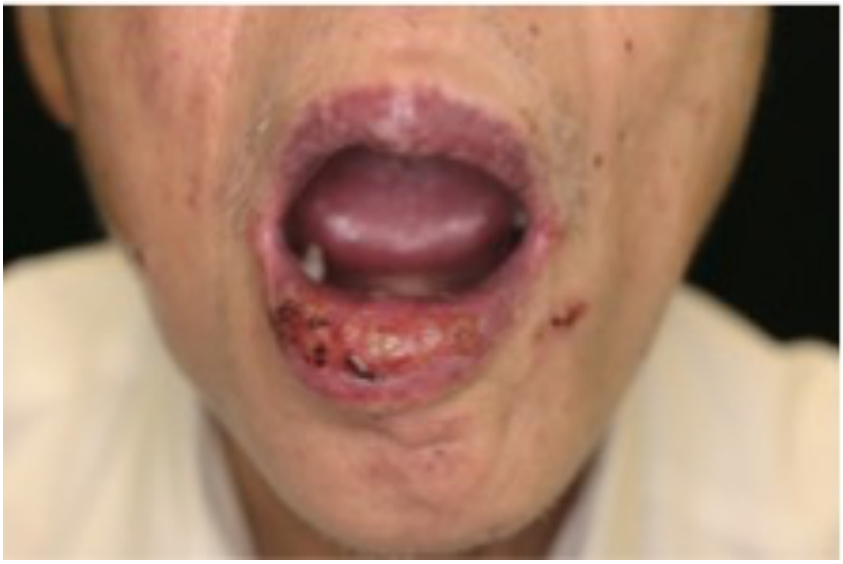
Case 27 – Basic Information and Clinical Findings

Patient: 70-year-old man
Chief complaint: Erosion and pain of the lower lip

History of present illness:
Two months before the initial visit, the patient became aware of erythema, erosion, and pain of the lower lip. He visited several nearby dermatology clinics and received topical antibacterial agents, oral and topical antihistamines, and topical steroids, but the condition worsened, leading to referral to our department for further evaluation and treatment.

Past medical history: Duodenal ulcer, type 2 diabetes mellitus (diet-controlled), hypertension, allergic rhinitis, left knee osteoarthritis
Medications: Amlodipine besylate
Social history: Smoked 30 cigarettes/day for 20 years (from age 20–40). History of occupational sun exposure as a schoolteacher. Dental metal fillings present (specific treatment period unknown).

Current findings:
Marked erythema, erosion, and crusting with partial hemorrhage were observed on the lower lip (Fig. 1). No mucosal lesions were found on the upper lip or oral cavity. No other skin lesions were noted on the body. Direct KOH examination of the lower lip lesion was negative.

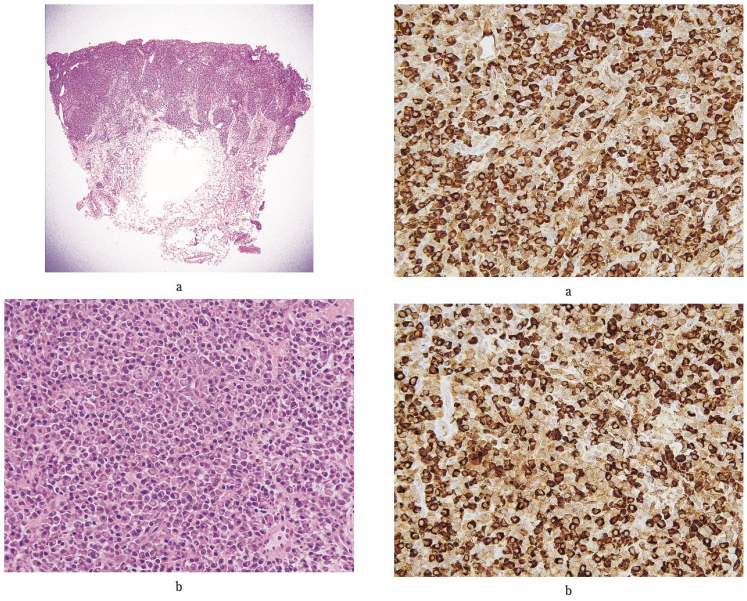


Case 27 – Laboratory and Histopathological Findings

Histopathological findings:
Most of the epidermis was lost and replaced by erosions, making the evaluation of epidermal atypia difficult. Dense infiltration of plasma cells extending from the superficial to mid-dermis was observed (Fig. 2a). Many infiltrating cells exhibited eccentric nuclei with a cartwheel appearance, consistent with plasma cells (Fig. 2b). No apparent atypical lymphoid cells were found. Immunohistochemistry demonstrated mixed populations of IgG-κ–positive and IgG-λ–positive plasma cells without light chain restriction (Fig. 3a, b).

Laboratory findings at presentation:
WBC 4,600/μL, RBC 4.71 × 10^6/μL, Hb 13.9 g/dL, PLT 207 × 10^3/μL, AST 15 IU/L, ALT 17 IU/L, LDH 143 IU/L, TP 6.9 g/dL, Alb 4.1 g/dL, BUN 14 mg/dL, Cr 0.68 mg/dL, Na 141 mEq/L, K 4.1 mEq/L, IgG 455.9 mg/dL, IgA 314 mg/dL, IgM 64 mg/dL, C3 98 mg/dL, C4 28 mg/dL.

Tests for ANA, anti-SS-A/SS-B antibodies, HBV surface antigen, HCV antibodies, TP antibodies, and HIV antibodies were all negative.

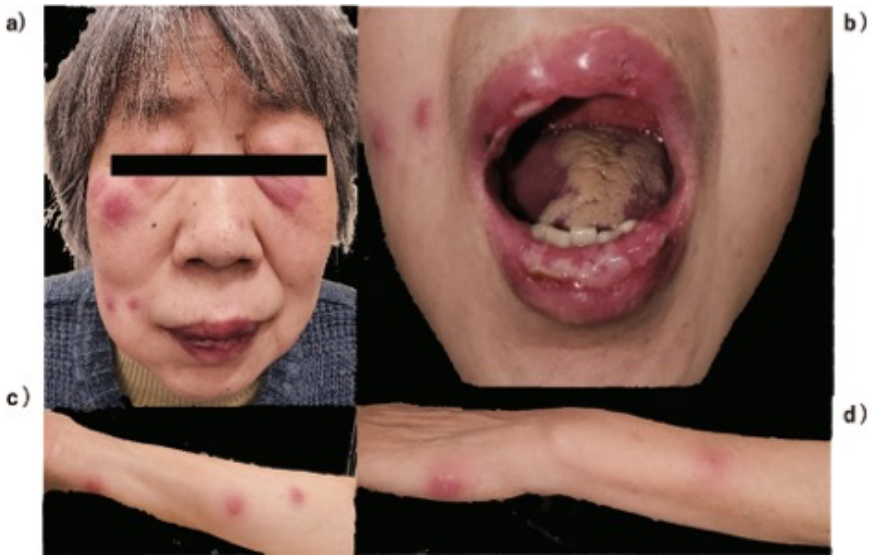


Case 28 – Basic Information and Clinical Findings

Patient: 67-year-old woman
Past medical history: Bronchial asthma, chronic otitis media
Medication history: None of note

History of present illness:
One week before presentation, the patient developed a fever up to 39°C accompanied by facial erythema. The following day, stomatitis, sore throat, and hoarseness appeared. She visited a nearby dermatology clinic and was suspected of having contact dermatitis, and betamethasone valerate/proprionate ointment was prescribed for facial lesions. However, her symptoms worsened, including oral mucosal pain and odynophagia, and she was referred to our department.

Current findings:
The patient was alert. Initial vitals were: temperature 38.8°C, blood pressure 130/64 mmHg, pulse 130/min, respiratory rate 18/min, SpO_2 94% (room air). Painful edematous erythematous plaques were scattered over the face and anterior neck. Multiple aphthous ulcers were present on the upper and lower lips and oral mucosa (Fig. 1a, b).



Case 28 – Laboratory and Imaging Findings

Laboratory findings:
WBC 15,990/μL (Neut 86.0%, Lym 6.1%, Mono 7.6%, Eos 0.1%)
RBC 4.10 × 10^6/μL, Hb 12.1 g/dL, Plt 363 × 10^3/μL
AST 26 U/L, ALT 16 U/L, LDH 171 U/L, ALP 103 U/L, γ-GTP 13 U/L

CK 82 U/L, BUN 26 mg/dL, Cre 0.44 mg/dL
CRP 18.71 mg/dL
sIL-2R 398 U/mL (reference 145–519)
ASO 45 IU/mL, RF 3 IU/mL, ANA <1:40
IgG 1,188 mg/dL, IgA 244 mg/dL, IgM 45 mg/dL
C3 180 mg/dL, C4 26 mg/dL, CH50 75.9 U/mL
Anti-SS-A antibody (−), anti-SS-B antibody (−)

HLA typing: A11, A24, B48, B54

PCR results at admission:
Negative for SARS-CoV-2, human coronaviruses 229E, HKU-1, NL63, OC43, influenza virus, adenovirus, enterovirus, rhinovirus, RS virus, Bordetella pertussis, Mycoplasma pneumoniae, Chlamydia species.

Bacterial cultures:
Throat culture negative, blood culture negative.

Imaging findings:
Contrast-enhanced cervical CT showed enlargement of right cervical lymph nodes without abscess formation

Histopathological findings:
A biopsy from the right cheek revealed subcorneal neutrophilic pustules and dense neutrophilic infiltration extending from the upper to mid dermis. No bacterial colonies were identified on HE staining (Fig. 3).

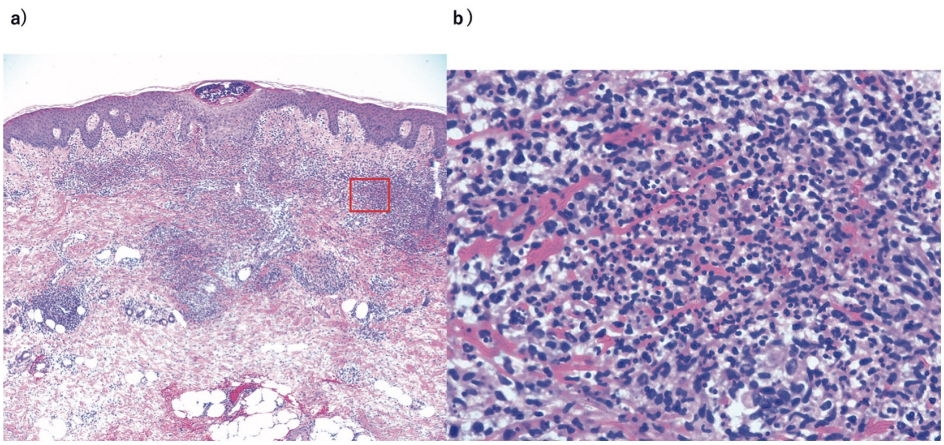


Fig. 3 Histopathological findings

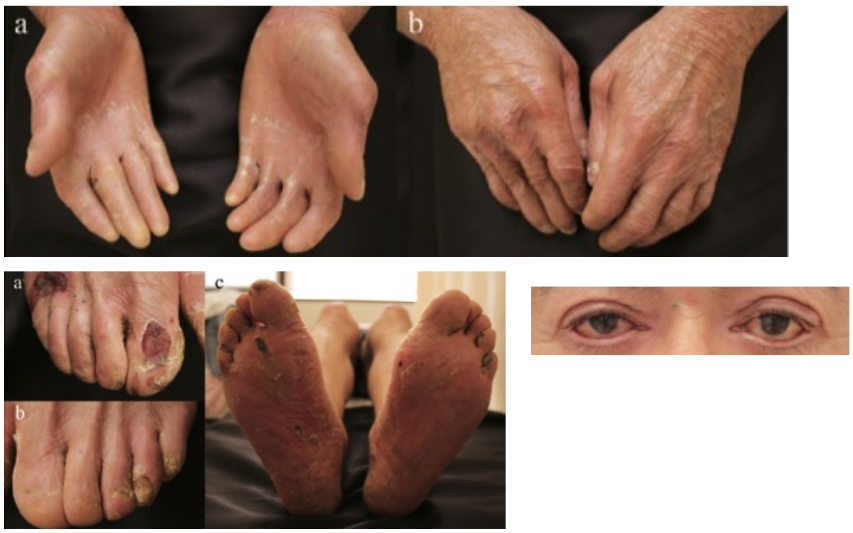
Case 29 – Basic Information and Clinical Findings

Patient: 53-year-old man
Chief complaint: Hand erosion, palmar blisters

History of present illness:
No abnormalities were noted at birth. Since early childhood, however, blisters appeared on the palms, elbows, and other pressure-prone sites, accompanied by erosion and crust formation. During elementary school, the toenails were lost. He worked in standing positions, but worsening plantar blister formation made continuing work difficult, leading to resignation. Because he wished to clarify the diagnosis, he consulted welfare services after resigning and was referred to our department.

Past medical history: Childhood asthma, diabetes mellitus (diagnosed at age 27), duodenal ulcer (diagnosed at age 49)
Family history: Possible similar blistering disorder (parents are second cousins; sibling is unaffected)

Current findings:
No external malformations of the lower limbs were observed, and no dental or hair abnormalities were noted.
The hands showed sclerotic contracture, shortened digits, and loss of fingernails.
Hemorrhagic blisters, erosions, and epidermal detachment were present.
No mucosal lesions or abnormal pigmentation were observed (Fig. 1–4).



Case 29 – Laboratory and Histopathological Findings

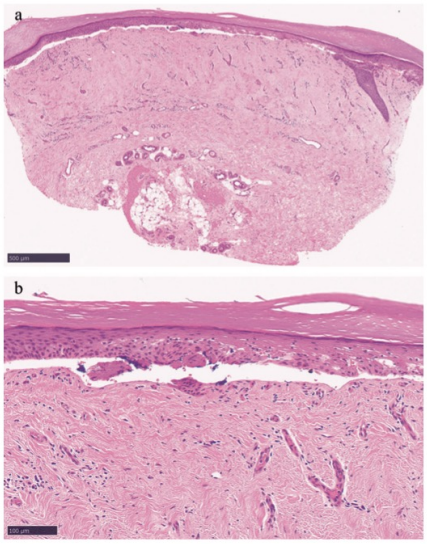
Histopathology 1:

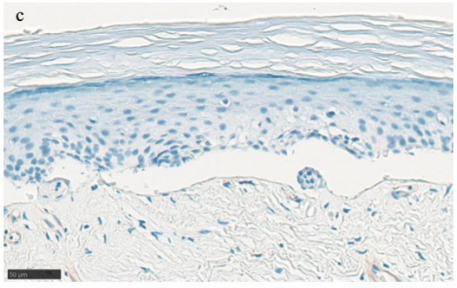
A biopsy was obtained from an induced blister on the right forearm after rubbing the skin.
The epidermis separated mostly at the basal layer, and partially within the spinous layer.
Spongiosis, hydropic degeneration, and intraepidermal vacuolar change were not seen.
Mild lymphocyte infiltration was noted in the upper dermis (Fig. 5a, b).
Immunofluorescence revealed type IV collagen deposition between the basal cells and the basement membrane (Fig. 5c).

Genetic testing 1 (Sanger sequencing, performed at age 52 on a previously collected sample):
Pathogenic variants in COL7A1 and FERMT1 were not detected.

Histopathology 2 (parafin-embedded skin biopsy performed at age 52):
Immunostaining for type IV collagen showed no abnormalities in either the patient or healthy control; no evidence of severe basement membrane degeneration consistent with Kindler syndrome was identified (Fig. 6).

Genetic testing 2 (Whole-exome sequencing performed at age 62):
A homozygous splice-site variant in COL7A1 (p.R1303Q/c.3908G>A) was detected (Fig. 7).
FERMT1, a known causative gene for Kindler syndrome, was normal.
Other blistering-related genes—KRT5, KRT14, PLEC, DST, EXPH5, CD151 (junctional EB), LAMA3, LAMB3, LAMC3, LAMA3A, ITGB4, ITGA6, ITGA3—were negative.
Thus, the COL7A1 variant was considered a pathogenic variant consistent with dystrophic epidermolysis bullosa.





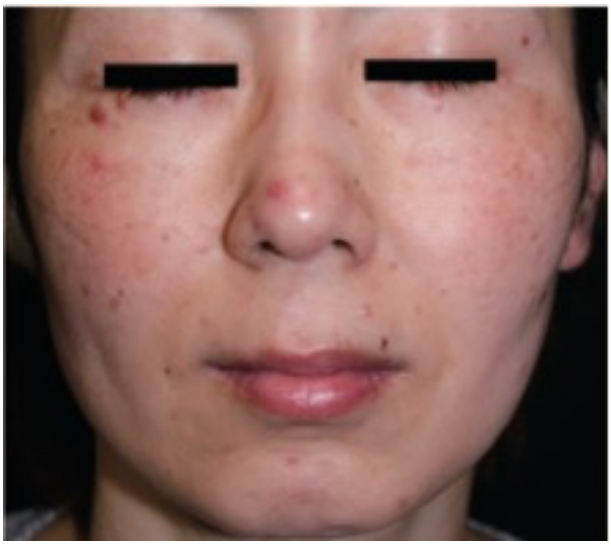
Case 30 – Basic Information and Clinical Findings

Patient: 42-year-old woman
Chief complaint: Facial eruptions

Past medical history: Alcohol-related pancreatitis (five episodes), multiple hepatocellular carcinomas treated at age 30
Comorbidities: Hypertension
Family history: Maternal aunt with rheumatoid arthritis, uncle with brain tumor

History of present illness:
Four months before presentation, the patient developed a right subconjunctival hemorrhage.
Three months before presentation, asymptomatic facial eruptions appeared, prompting referral to our department.

Current findings:
Multiple millimeter-sized erythematous papules were scattered over the lower eyelids, nasal ala, cheeks, and mandibular region (Fig. 1).



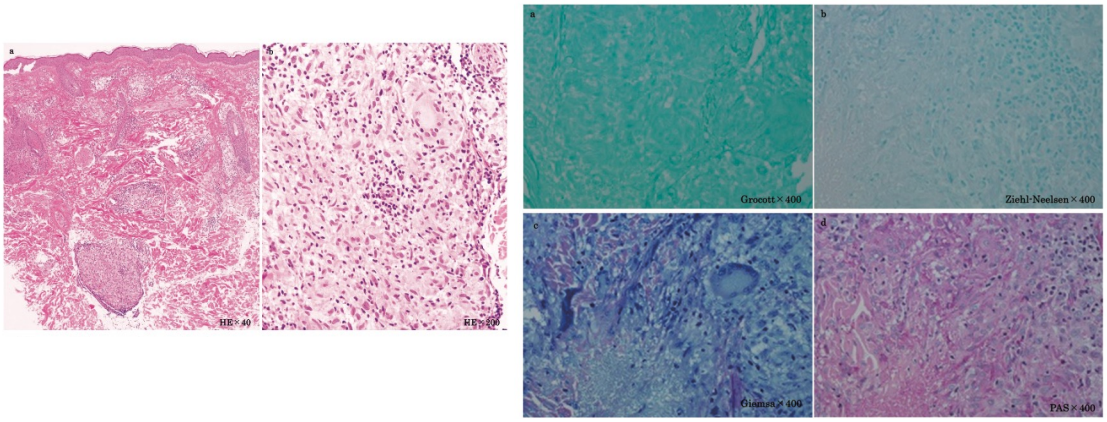
Case 30 – Laboratory and Imaging Findings

Histopathological findings:
A biopsy from an erythematous papule on the left mandibular region revealed multiple naked granulomas with Langhans-type multinucleated giant cells in the dermis (Fig. 2a, b).
Grocott, Ziehl–Neelsen, Giemsa, and PAS stains were negative for fungi and mycobacteria (Fig. 3a–d).

Laboratory findings:
WBC 4,200/μL, RBC 4.13 × 10^6/μL, Hb 11.9 g/dL, Plt 121 × 10^3/μL
AST 31 U/L, ALT 21 U/L, ALP 260 U/L
Cre 0.64 mg/dL, CRP 0.13 mg/dL
Ca 9.2 mg/dL, ACE 10.8 U/L
Anti-cardiolipin β2-glycoprotein I complex antibody (aCLβ2GPI) 8.9 U/mL (reference 0–3.5)
Lupus anticoagulant: LA1 32.0 (0–1.16)
Anti-SS-A antibody 148 U/mL (0–10), anti-SS-B antibody 26.7 U/mL (0–10)
Rheumatoid factor 20 U/mL (0–15)
PT 14.9 sec (10.5–13.5), APTT 12.6 sec
TARC 1,200 pg/mL
sIL-2R 428.3 U/mL
Serum protein electrophoresis: no M-protein spike
IgG was repeatedly ≥12 g/dL after 2 weeks, indicating polyclonal hypergammaglobulinemia.

Imaging findings:
Chest CT revealed bilateral hilar and mediastinal lymphadenopathy and multiple small nodules scattered throughout the lungs (Fig. 4a, b).
Abdominal ultrasound revealed hepatosplenomegaly.

Other examinations:
Holter ECG and nerve conduction studies showed no abnormalities.
Schirmer test and fluorescein staining of the eyes were negative.



The original questionnaire was administered in Japanese. For publication, the Japanese questionnaire items and AI-generated responses were translated into English.

Case 1
Differential Diagnosis:
- Malignant melanoma
- Pigmented nevus
- Pigmented basal cell carcinoma

Key Points for Differentiation:
Malignant melanoma is most suspicious due to its variegated pigmentation and asymmetry; dermoscopic findings such as shiny white lines and structureless areas also support this. A definitive diagnosis requires excisional biopsy and histopathology. Pigmented nevus typically presents in younger patients and remains stable; dermoscopic structures that are regular support this diagnosis. Basal cell carcinoma may show shiny white structures, but the color and morphology in this case make it less likely.

Case 2
Differential Diagnosis:
- Seborrheic keratosis
- Superficial basal cell carcinoma
- Malignant melanoma

Key Points for Differentiation:
Seborrheic keratosis is considered because of leaf-like areas and telangiectasia, but the lesion's asymmetric and enlarging nature argues against it. Basal cell carcinoma is also a differential due to telangiectasia and surface irregularity. Malignant melanoma remains difficult to exclude because of color variegation and irregular borders. Confirmation requires biopsy and dermoscopic evaluation, including assessment for milia-like cysts, blue-gray ovoid nests, and the pattern of melanin distribution.

Case 3
Differential Diagnosis:
- Squamous cell carcinoma (SCC)
- Bowen's disease
- Condyloma acuminatum

Key Points for Differentiation:

A long-standing elevated lesion with ulceration in an immunosuppressed patient strongly suggests SCC. Bowen's disease is also a consideration because of the chronic erythematous plaque. Condyloma acuminatum may be considered if multiple papules are present. Definitive diagnosis requires biopsy to evaluate atypical keratinocytes and basement membrane invasion; HPV-PCR positivity for types 6/11 would support condyloma.

Case 4
Differential Diagnosis:
- Melanocytic nevus
- Malignant melanoma
- Palmoplantar pigmentation with hyperkeratosis

Key Points for Differentiation:
A raised, dark-brown lesion on the palm accompanied by a parallel pattern favors melanocytic nevus. Malignant melanoma cannot be fully excluded due to elevation and possible enlargement; the absence of irregular streaks and blue-white veil supports exclusion. Hyperkeratotic pigmentation is a consideration but is unlikely given the raised morphology. Excisional biopsy is required to assess junctional activity and cytologic atypia.

Case 5
Differential Diagnosis:
- Cutaneous metastasis
- Subcutaneous lymph node metastasis
- Cutaneous soft tissue tumor (e.g., liposarcoma)

Key Points for Differentiation:
Given the patient's cancer history, rapid enlargement of a subcutaneous mass, and high uptake on PET-CT, cutaneous metastasis is most suspected. Subcutaneous lymph node metastasis is also a consideration but requires correlation with inguinal or pelvic lymph node findings. Soft-tissue tumors such as liposarcoma are possible but typically lack bilateral symmetry. Confirmation requires core-needle or excisional biopsy.

Case 6
Differential Diagnosis:
- Bowen's disease
- Psoriasis vulgaris
- Contact dermatitis

Key Points for Differentiation:
An erythematous lesion with a whitish background and dotted/glomerular vessels strongly suggests Bowen's disease. Psoriasis is characterized by scales and symmetry but is unlikely due to the patient's age and the solitary lesion. Contact dermatitis is unlikely because of the poor steroid response and chronic course. Biopsy is needed to evaluate atypical keratinocytes and vascular proliferation in the papillary dermis.

Case 7
Differential Diagnosis:
- Primary cutaneous diffuse large B-cell lymphoma (DLBCL)
- Primary cutaneous peripheral T-cell lymphoma (PTCL)
- Cutaneous metastasis

Key Points for Differentiation:
A firm, elastic, mobile, reddish nodule with ulceration and multiple bilateral involvement suggests DLBCL. PTCL is also a differential but is unlikely if T-cell markers are negative. Cutaneous metastasis must be considered, but in the absence of a detectable primary tumor on systemic evaluation, it becomes unlikely. Biopsy with immunohistochemistry (CD20, CD3, Ki-67) is essential.

Case 8
Differential Diagnosis:
- Necrotizing fasciitis
- Erysipelas
- Cellulitis

Key Points for Differentiation:
Acute onset, fever, extensive erythema and swelling, and marked firmness of the subcutis most strongly indicate necrotizing fasciitis. Erysipelas typically presents with sharply demarcated erythema on the face, which does not match this case. Cellulitis is also considered, but the pronounced induration below the fascia makes it less likely. Diagnosis requires contrast-enhanced CT or MRI to evaluate fascial involvement, along with surgical confirmation of necrosis.

Case 9
Differential Diagnosis:
- Extramammary Paget's disease (EMPD)
- Superficial basal cell carcinoma
- Chronic eczema

Key Points for Differentiation:
Symmetric erythema, infiltration, and scaling in the genital or axillary region with long-standing symptoms and lymphadenopathy favor EMPD. Superficial BCC typically presents with localized pigmentation or ulceration, which differs from this case. Chronic eczema is less likely due to the absence of lymphadenopathy and poorly defined borders. Skin biopsy confirming Paget cells and CK7 positivity is required.

Case 10
Differential Diagnosis:
- Lipoma
- Fibroma
- Subcutaneous cyst (e.g., epidermal cyst)

Key Points for Differentiation:
A soft, elastic, mobile subcutaneous mass with a smooth surface most strongly suggests lipoma. Fibroma is a consideration but tends to be firmer with limited mobility. Subcutaneous cysts often show a central punctum or inflammation, which is absent here. Ultrasound showing homogeneous low echogenicity and MRI demonstrating T1-high signal with fat suppression support the diagnosis.

Case 11
Differential Diagnosis:
- Glomus tumor
- Myxoid cyst
- Subungual squamous cell carcinoma (SCC)

Key Points for Differentiation:
A small yellow–white nodule with pain at the nail fold strongly suggests a glomus tumor. Myxoid cysts often arise from pressure on the nail matrix but typically present with minimal pain. Subungual SCC may show ulceration or destructive changes as it progresses, but in this case the lesion is small and localized. Confirmation requires MRI demonstrating high-signal findings and biopsy showing proliferation of perivascular smooth muscle cells.

Case 12
Differential Diagnosis:
- Cutaneous metastasis
- Paronychia/abscess
- Subungual squamous cell carcinoma (SCC)

Key Points for Differentiation:
Given the history of pulmonary squamous cell carcinoma, rapid progression, erosion, ulceration, and bleeding, cutaneous metastasis is most strongly suspected. Paronychia may also present with inflammation and swelling but is unlikely due to the tumor-like enlargement and persistent course. SCC is a differential, but the patient's history and multiplicity favor metastasis. Biopsy demonstrating metastatic squamous carcinoma with immunohistochemical concordance with the primary tumor is required for confirmation.

Case 13
Differential Diagnosis:
- Prurigo nodularis with secondary amyloidosis
- Cutaneous tuberculosis (particularly verrucous tuberculosis)
- Chronic ulcer associated with connective tissue disease (e.g., dermatomyositis)

Key Points for Differentiation:
Prurigo nodularis with amyloidosis presents with chronic scratching leading to mixed nodules and pigmentation, often on the extremities. Cutaneous tuberculosis shows chronic ulceration with surrounding scar-like changes and slow progression. Connective-tissue–disease–related ulcers often have systemic findings such as Raynaud's phenomenon or positive autoantibodies. Skin biopsy can reveal amyloid deposition, specific granulomas, or vasculitis. Additional testing such as blood work, tuberculin testing, or QFT is useful for differentiation.

Case 14
Differential Diagnosis:
- Lipoma
- Subcutaneous soft tissue tumor (e.g., schwannoma)
- Primary cutaneous lymphoma

Key Points for Differentiation:
A subcutaneous mass that is soft-to-firm in elasticity with a relatively smooth surface suggests lipoma. Soft tissue tumors such as schwannoma should also be considered, particularly if tenderness or neurologic symptoms are present. Primary cutaneous lymphoma may be considered if erythematous nodules or symmetric lesions are present. Ultrasound or MRI evaluation of internal structure, and biopsy when necessary, help distinguish adipocytes from tumor cells.

Case 15

Differential Diagnosis:
- Subcutaneous liposarcoma
- Subcutaneous fibrosarcoma
- Subcutaneous abscess

Key Points for Differentiation:
Gradual enlargement over a long period followed by rapid swelling, erythema, warmth, and hemorrhagic nodules in the excised specimen make liposarcoma the leading suspicion. Fibrosarcoma is also a differential based on firm induration with poor mobility. Abscess is less likely due to the chronic course and recurrent nature, as abscesses typically present acutely with fluctuance. MRI to confirm fatty components and biopsy demonstrating atypical adipocytes or fibrous tumor cells are essential for diagnosis.

Case 16
Differential Diagnosis:
- Drug-induced bullous disorder (e.g., immunotherapy-related bullous pemphigoid)
- Pemphigus vulgaris
- Impetigo

Key Points for Differentiation:
Given the history of nivolumab administration and the presence of widespread erythema with tense bullae, a drug-induced bullous disorder is most strongly suspected. Pemphigus vulgaris may also cause multiple bullae, but in an elderly male with a cancer history, a drug-induced etiology is more likely. Impetigo typically presents with localized lesions, which does not match the generalized and chronic course in this case. Confirmation requires skin biopsy showing subepidermal blister formation, direct immunofluorescence demonstrating BP180 deposition, and serum anti-BP180 antibody testing.

Case 17
Differential Diagnosis:
- Herpes zoster
- Varicella
- Drug eruption

Key Points for Differentiation:
A T10–L3 dermatomal distribution with pain and clusters of small vesicles strongly suggests herpes zoster. Varicella also presents with vesicles but typically shows generalized distribution, making it unlikely here. Drug eruptions often present symmetrically and may involve mucous membranes, which does not match this vesicle-dominant presentation. Confirmation is aided by Tzanck smear showing multinucleated giant cells or positive VZV-PCR.

Case 18
Differential Diagnosis:
- IgA vasculitis (Henoch–Schönlein purpura)
- Cryoglobulinemic vasculitis
- Drug-induced purpura

Key Points for Differentiation:
A young male with palpable purpura on the extremities, lower-leg pain, and oral mucosal lesions most strongly suggests IgA vasculitis. Cryoglobulinemic vasculitis is also considered, but systemic symptoms and arthralgia are less supportive in this case. Drug-induced purpura is generally symmetric and lacks tenderness or ulceration, making it unlikely. Skin biopsy showing IgA deposition in vessel walls and elevated serum IgA levels support the diagnosis.

Case 19
Differential Diagnosis:
- Dermatomyositis
- Atopic dermatitis
- Psoriasis vulgaris

Key Points for Differentiation:
V-neck sign, Gottron's sign, reticular erythema on the extremities, and proximal muscle weakness strongly indicate dermatomyositis. Atopic dermatitis is characterized by excoriations and xerosis without muscle symptoms. Psoriasis typically presents with symmetric lesions on the elbows and knees with silvery scales, differing from this case. Confirmation includes elevated serum muscle enzymes, anti-ARS antibodies, EMG findings, and muscle biopsy showing inflammatory myopathy.

Case 20
Differential Diagnosis:
- Subcutaneous abscess
- Cellulitis
- Deep vein thrombosis (DVT)

Key Points for Differentiation:
A subcutaneous abscess is most strongly considered because of localized tenderness, swelling, and firm induration with associated erythema and pain. Cellulitis presents with widespread erythema and tenderness but typically lacks a focal firm nodule. DVT can present with pain and swelling but generally does not show erythema. Ultrasound evaluation for abscess cavity or thrombosis, along with inflammatory markers and D-dimer testing, aids in differentiation.

Case 21
Differential Diagnosis:
- Achromic psoriasis
- Dermatomyositis
- Flat warts

Key Points for Differentiation:
Achromic psoriasis is consistent with this case because of non-pruritic reddish-brown papules scattered on the extremities and trunk. Dermatomyositis can also present with violaceous papules on the extremities and trunk, but muscle weakness and positive antinuclear antibodies help distinguish it. Flat warts are viral and often present as clusters of brownish papules; dermoscopy showing dilated capillaries and loss of normal skin markings, as well as biopsy demonstrating hyperkeratosis and viral changes, aid in differentiation.

Case 22
Differential Diagnosis:
- Peripheral arterial disease due to arteriosclerosis obliterans (ASO)
- Buerger's disease (thromboangiitis obliterans, TAO)
- Diabetic foot ulcer

Key Points for Differentiation:
ASO typically occurs in older patients with atherosclerotic risk factors (smoking, diabetes, hypertension, hyperlipidemia) and presents with lower-limb coldness, intermittent claudication, and distal ulcers; ABI reduction and vascular ultrasound are useful for evaluation. In this case, heavy smoking and coldness at the ulcer site strongly suggest ASO. Buerger's disease is more common in young to middle-aged heavy smokers and is characterized by ischemic ulcers of the distal extremities, sometimes accompanied by migratory thrombophlebitis. Diabetic foot ulcers are usually painless and associated with neuropathy, peripheral circulatory disturbance, and infection. Considering the severe pain and smoking history, ASO or TAO is most strongly suspected, and angiography and ABI measurements are important for differentiation.

Case 23
Differential Diagnosis:
- Necrotizing fasciitis
- Deep vein thrombosis (DVT)
- Cellulitis

Key Points for Differentiation:
Necrotizing fasciitis is characterized by rapidly progressive violaceous edema, necrosis, severe pain, and systemic deterioration, making it the leading consideration in this case. DVT can also cause swelling and pain, but erythema and blister formation are usually minimal. Cellulitis typically presents with local warmth and

erythema, but systemic symptoms are generally milder. Contrast-enhanced CT to evaluate fascial thickening or gas formation, ultrasound to detect thrombosis, and blood cultures or fascial biopsy are important for definitive diagnosis.

Case 24
Differential Diagnosis:
- Tinea faciei
- Rosacea-like dermatitis
- Contact dermatitis

Key Points for Differentiation:
Tinea faciei presents with annular erythema accompanied by peripheral pustules and scales; a history of cat ownership and exacerbation with antibiotics also support this diagnosis. Rosacea-like dermatitis causes erythema and scaling around the nose but less commonly shows clearly marginated lesions with peripheral predominance and pustules. Contact dermatitis is considered based on exposure history and distribution corresponding to contact areas. Diagnosis is confirmed by KOH direct microscopy and fungal culture.

Case 25
Differential Diagnosis:
- Linear lichen sclerosus
- Morphea
- Superficial fungal infection

Key Points for Differentiation:
Linear lichen sclerosus is characterized by linear erythema and sclerosis along the lines of Blaschko, often with minimal pruritus, consistent with this case. Morphea (localized scleroderma) also presents with sclerotic erythematous plaques but tends to show deeper sclerosis, atrophy, and depigmentation. Superficial fungal infection typically has erythema and scaling accentuated at the lesion margins, and fungi are detected on KOH examination. Skin biopsy and KOH direct microscopy are useful for differentiation.

Case 26
Differential Diagnosis:
- Allergic contact dermatitis
- Palmoplantar pustulosis
- Chronic eczema

Key Points for Differentiation:
Allergic contact dermatitis is most strongly considered because of erythema, swelling, and small vesicles on both dorsal hands and the face; even with negative patch tests, a delayed-type hypersensitivity reaction to an unidentified allergen remains possible. Palmoplantar pustulosis characteristically presents with pustular erythema on the palms and soles, often associated with plantar lesions and joint pain, with facial involvement being rare. Chronic eczema generally shows bilateral symmetric erythema and scaling, but acute pustules are uncommon. Skin biopsy demonstrating dermal edema and intraepidermal pustules, along with blood tests for IgE and eosinophils, helps in differentiation.

Case 27
Differential Diagnosis:
- Actinic cheilitis
- Allergic contact cheilitis
- Lichen planus of the lip

Key Points for Differentiation:
Actinic cheilitis preferentially affects elderly men with long-term ultraviolet exposure and presents with erythema, erosion, and scaling localized to the lower lip; this case is consistent given the history of smoking, UV exposure, and chronic course. Allergic contact cheilitis is caused by metals, dental materials, cosmetics, and similar agents, producing erythema and erosion limited to areas of allergen contact; the presence of dental metals in this case makes patch testing useful. Lichen planus of the lip typically shows well-demarcated white reticular lesions and may involve the oral mucosa. Fungal infection is unlikely given negative KOH, and biopsy is important for histopathologic diagnosis.

Case 28
Differential Diagnosis:
- Behçet’s disease
- Stevens–Johnson syndrome (SJS)
- Herpes simplex virus infection

Key Points for Differentiation:
Behçet’s disease is characterized by recurrent oral aphthae, genital ulcers, ocular lesions, and skin manifestations such as erythema nodosum, often with multisystem involvement. In this case, facial and limb erythema and multiple oral aphthae raise suspicion. SJS presents with high fever followed by rapidly progressive erythema and erosions, and a detailed drug history is crucial; in this case, there is a history of topical steroids and NSAIDs but no notable systemic drug exposure. Herpes simplex infection causes localized vesicles and erosions with severe pain and a predilection for recurrent, localized lesions; however, the

widespread distribution in this case makes it less likely. Blood tests, HLA-B51 typing, and histopathological evaluation are useful for definitive diagnosis.

Case 29
Differential Diagnosis:
- Dystrophic epidermolysis bullosa (DEB)
- Junctional epidermolysis bullosa (JEB)
- Hereditary palmoplantar keratoderma

Key Points for Differentiation:
DEB typically presents from birth or early childhood with blisters at sites of mechanical trauma, followed by scarring, nail loss, and digital shortening, often with a positive family history, all of which fit this case. JEB, especially severe infantile forms, shows generalized blisters and erosions in infancy, with additional features such as dental enamel defects and hair abnormalities, which are absent here. Hereditary palmoplantar keratoderma mainly manifests as localized keratotic plaques, and blistering or scarring is rare. Considering childhood onset, scarring, nail loss, digital shortening, and family history together, DEB is most strongly suspected. Electron microscopy, immunostaining of skin biopsy, and genetic analysis are essential for confirmation.

Case 30
Differential Diagnosis:
- Rosacea
- Dermatomyositis
- Systemic lupus erythematosus (SLE)

Key Points for Differentiation:
Rosacea is characterized by chronic, usually asymptomatic erythematous papules and pustules on the central face. Dermatomyositis may show facial erythema and edema accompanied by proximal muscle involvement, but in this case there are no muscle symptoms, making it unlikely. SLE often presents with a malar rash, photosensitivity, and systemic manifestations such as arthralgia, which are absent here. Past medical and family history together with serological tests (antinuclear antibodies, muscle enzymes) help differentiate these conditions.