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CASE REPORT

Rie Tabata · Chiharu Tabata · Shunzo Namiuchi
Makoto Terada · Ryoji Yasumizu · Tomoko Okamoto · Tomoko Nagai

Adult T-cell lymphoma mimicking Henoch–Schönlein purpura

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Abstract We report a male patient with adult T-cell lymphoma, who was initially diagnosed clinically as having Henoch–Schönlein purpura (HSP) with abdominal pain and specific purpura. Adult T-cell lymphoma-like cells were minimal and abdominal lymph nodes were transiently swollen, and the symptoms were improved by supportive management. Although the clinical course was compatible with HSP, the histological examination revealed infiltration of lymphocytes rather than neutrophils. Later he developed lymphoma and was treated with chemotherapy. This rare case suggests the importance of skin biopsies to seek the underlying pathology in adult HSP.

Key words Adult T-cell lymphoma · Henoch–Schönlein purpura

Introduction

Henoch–Schönlein purpura (HSP) is a systemic vasculitis characterized by the tissue deposition of IgA containing immune complexes mainly in the vessels in the skin, gastrointestinal tract, and glomeruli. The histological findings show leukocytoclastic or necrotizing angiitis in small-sized vessels. The characteristic symptoms include specific nonthrombocytopenic palpable purpura with angioedema, arthralgia, abdominal pain, and glomerulonephritis, and HSP typically runs a benign self-limited course. In most cases the diagnosis is clinically established when at least two of the following four criteria by the American College of Rheumatology (ACR)[1] are present: (1) palpable purpura, (2) age <20 years at disease onset, (3) bowel angina, and (4) wall granulocytes on biopsy. It is mainly a disease of children and young adults as commonly occurs in those aged 2–11 years, with an incidence of 14 per 1 million people.[2] In adult cases of HSP, malignant diseases are sometimes associated, and a careful search for the underlying disease is needed. Here we report a patient who was clinically diagnosed as having HSP with typical palpable purpura, abdominal colicky pain, and occult blood in urine, but 1 month later developed adult T-cell lymphoma (ATL), which was diagnosed prior to the clinically apparent state by the clonal HTLV-I proviral integration in biopsied small lymph node without histologically proven malignant lymphoma.

Case report

A 76-year-old man was admitted owing to appetite loss, abdominal pain, and body weight loss. He had been suffered from symptoms for an infection of upper respiratory tract and treated with antibiotics prior to the onset of abdominal symptoms. Gastrointestinal and colonic fiberscopic examinations revealed multiple ulcers both in the stomach (Fig. 1A) and colon. *Helicobacter pylori* were detected, and the combination of amoxicillin, clarithromycin, and lansoprazole was administered. Three days later, edema and multiple palpable purpura of 2–3 mm diameter appeared in the bilateral lower extremities, and a diagnosis of HSP was made.

Upon admission, he had a temperature of 37.2ºC, reddening of the throat, surface lymph nodes of smaller than 1 cm in a diameter in the bilateral cervical, axillary, and left inguinal regions, but neither hepatosplenomegaly nor subcutaneous nodules were present. The swelling of abdominal

R. Tabata (✉) · S. Namiuchi · M. Terada · T. Nagai
[a]Department of Internal Medicine, Hyogo Prefectural Tsukaguchi Hospital, 6-8-17 Minamitsukaguchi, Amagasaki, Hyogo 661-0012, Japan
Tel. +81-6-6429-5321; Fax +81-6-6422-7405
e-mail: ctabata@kuhp.kyoto-u.ac.jp

R. Yasumizu
Division of Pathology, Hyogo Prefectural Tsukaguchi Hospital, Hyogo, Japan

T. Okamoto
Department of Gastroenterology, Hyogo Prefectural Tsukaguchi Hospital, Hyogo, Japan

C. Tabata
HMRO, Graduate School of Medicine, Kyoto University, Kyoto, Japan

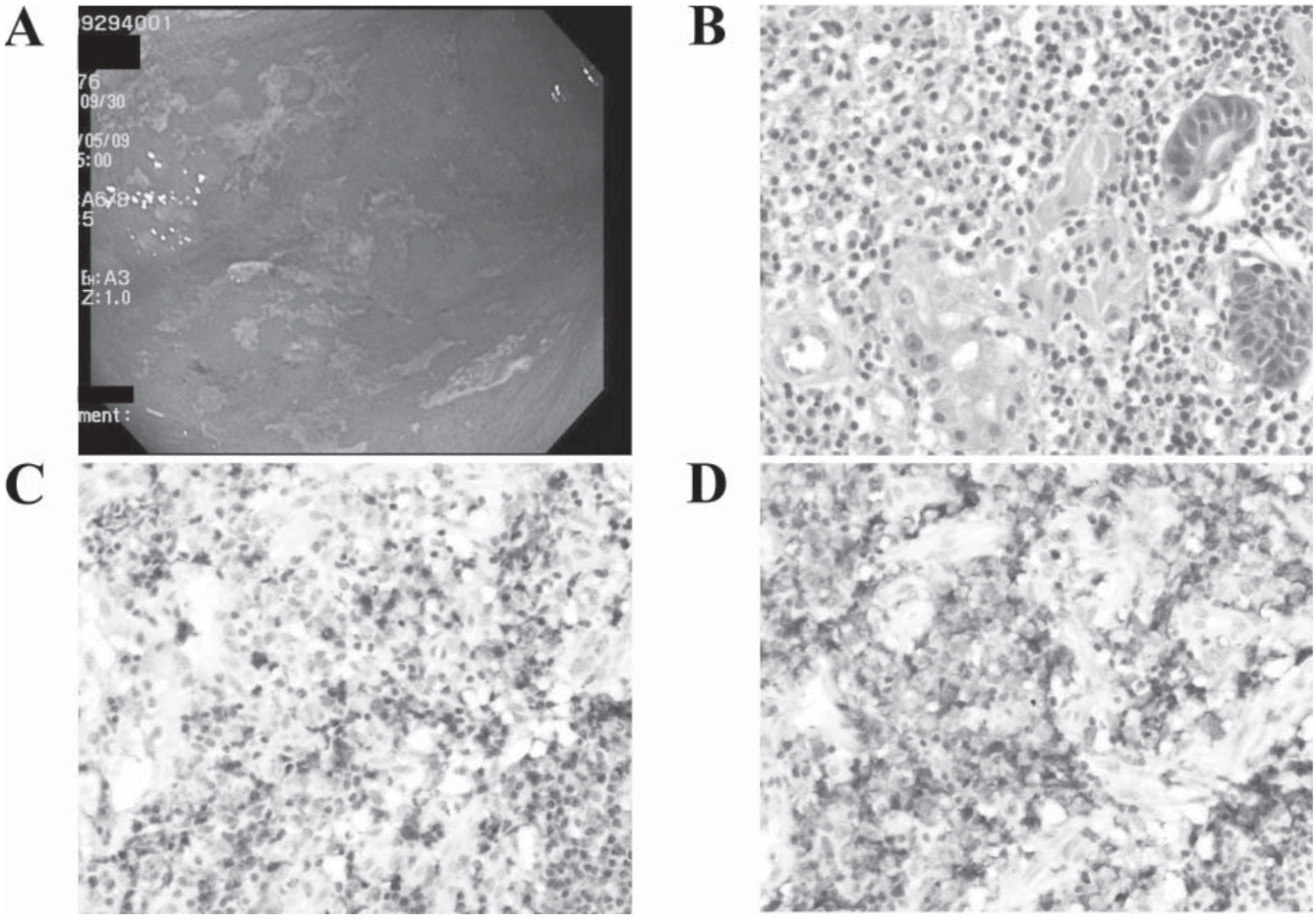

Fig. 1A–D. Gastrointestinal fiberscopic examination. **A** Multiple erosions and ulcers were demonstrated in the stomach. **B** Histological examination revealed that small lymphocytes were infiltrated to the mucosa (H&E staining, ×100). Many of them showed negative staining for L26 (**C**, ×100) and positive staining for UCHL-1 (**D**, ×100)

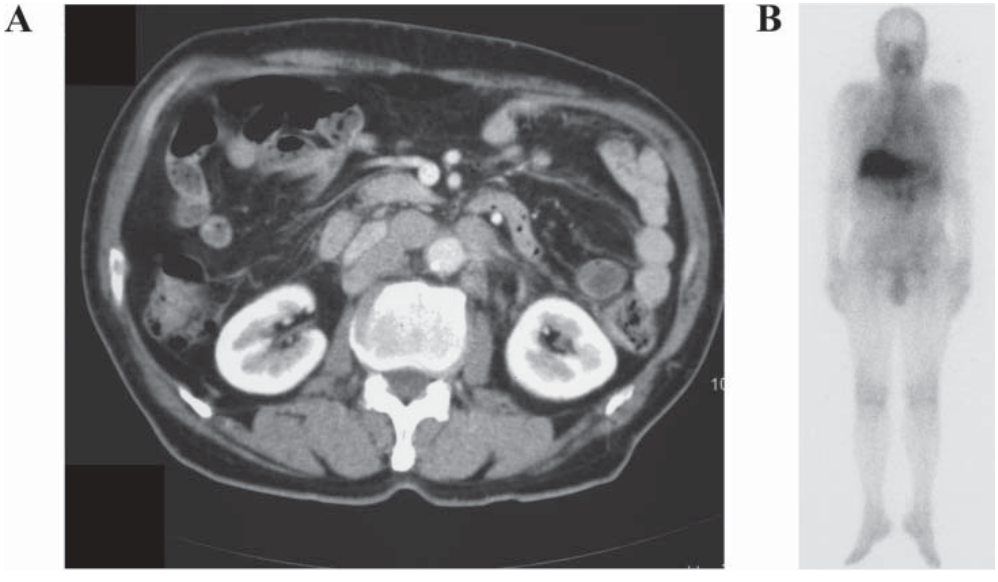

Fig. 2. Swelling of abdominal lymph nodes (approximately 1 cm in diameter) was demonstrated by abdominal computed tomography (**A**) and gallium scintigraphy (**B**), which disappeared spontaneously

lymph nodes of 1 cm diameter was demonstrated by abdominal computed tomography (CT) and the activity was proven by gallium scintigraphy (Fig. 2). Laboratory findings (Table 1) revealed markedly elevated levels of alkaline phosphatase (ALP, 624 IU/l) and lactic dehydrogenase (LDH, 1388 IU/l). The serum immunoglobulin levels including IgG, IgA, and IgM were within the normal range (1793, 392, and 48 mg/dl, respectively). Although blood cell

Table 1. Laboratory findings on admission

WBC	5800/ml	GOT	42 IU/l	HTLV-1 Ab	(WB)(+)
Neu	53%	GPT	23 IU/l	sIL-2R	3882 U/ml
Ly	22%	ALP	624 IU/l	KL-6	1400 U/ml
Mo	17%	LDH	1388 U/l	ANA	×80
Aty Ly	5%	γGTP	74 IU/l	CH50	53.8 U/ml
RBC	447×10^4/ml	BUN	10.3 mg/dl	PR3-ANCA	3.1 U/ml
Hb	12.9 g/dl	Cr	0.78 mg/dl	MPO-ANCA	<3.1 U/ml
Ht	39.3%	UA	6.9 mg/dl	Ccr	63.5 ml/min
PLT	38.1×10^4/ml	ALB	3.6 g/dl	Urinalysis	
PT	138%	Ca	9.5 mg/dl	Blood (+), protein (±)	
APTT	31 s	CRP	1.1 mg/dl	Fecal occult blood (+), (+)	
Fib	286 mg/dl	IgG	1793 mg/dl	PBMC surface marker	
D-D	1.40 mg/ml	IgA	392 mg/dl	CD3	69.7%
		IgM	48 mg/dl	CD4	32.3%
				CD8	41.7%

counts were normal, 5% of abnormal lymphocytes were demonstrated. The urinalysis was positive for occult blood and protein, which was improved 1 month later, and the data relating to renal function including blood urea nitrogen, creatinine, and creatinine clearance test were normal. Occult blood was also detected in the feces. Positive reaction for human T-cell leukemia/lymphoma virus type I (HTLV-I) was proven by Western blotting, and soluble interleukin-2 receptor (sIL-2R) was highly elevated (3882 U/ml). The abnormal lymphocytes seen in the peripheral blood were small lymphocytes with a convoluted nucleus, although they were rare and transiently observed. The typical "flower cell" character was absent, and surface markers for peripheral lymphocytes disclosed no particular increase of CD4(+) cells.

One week later, his symptoms including leg edema, skin purpura, and abdominal pain had disappeared following bed rest and treatment with carbazochrome sodium sulfonate and ascorbic acid. At the same time, the gastric ulcers and the swollen lymph nodes in the abdomen ameliorated, and a smoldering type of ATL was diagnosed with the following laboratory findings: lymphocyte count in the peripheral blood <4000, with >5% of abnormal lymphocytes, almost normal levels of LDH and serum calcium, and peripheral lymph nodes becoming small. The sIL-2R level was also decreased (1941 U/ml). Histological examination of lymph nodes (Fig. 3A–C) revealed slightly fibrotic changes with normal structure of follicles. A small fraction of large lymphoblast-like cells with positive reactivity for CD3 was detected in the medullary sinus. Although the histological findings for malignant lymphoma were not demonstrated, the monoclonal HTLV-I proviral integration was proven by Southern blot analysis (Fig. 3D). Furthermore, we performed a precise investigation on biopsied specimens from the skin and gastric mucosa. Invasion of plasma cells and small lymphocytes was detected in the gastric mucosa (Fig. 1B) with scarcely observed lymphoepithelial lesion (LEL), which is frequently observed in gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Mainly the lymphocytes were composed of UCHL-1(+) L26(–) cells (Fig. 1C,D). The histological findings of the skin (Fig. 4) revealed infiltration of UCHL-1(+) L26(–) lymphocytes, not neutrophils, around the vessels in the upper derma, which differed from the specific findings for HSP. Deposition of IgA was not confirmed around the vessels in the specimen embedded in paraffin (data not shown).

After follow-up without medication for a month, the patient was readmitted with swelling of surface lymph nodes of 1 cm in diameter with elevated levels of ALP (931 IU/l), LDH (481 IU/l), sIL-2R (5102 U/ml), and calcium (13.1 mg/dl). Although the surface lymph nodes were small and the number of peripheral abnormal lymphocytes had not increased, we immediately started chemotherapy for lymphoma type ATL with previous confirmation of the clonal expansion of ATL cells in the lymph node during the first admission. Because he suffered from severe adverse effects on conventional combined chemotherapy, and with due consideration for his older age, it was decided that he would receive more mild chemotherapy with oral administration of low doses of etoposide and steroid. Gradually the lymphoma cells became resistant to chemotherapy, and he died of hypercalcemia 9 months after the first admission.

Discussion

In our patient, at presentation typical symptoms were present and fulfilled two of the four criteria of ACR for HSP and four (palpable edema, bowel angina, GI bleeding, and hematuria) of the six criteria of Michel.[3] His symptoms and abnormal laboratory findings were ameliorated by bed rest and supportive therapy alone for a week. Only small nonspecific surface lymph nodes were palpable at the first admission. Although the diagnosis of HSP had been made based on his clinical symptoms and the self-limiting course, we performed further studies to evaluate underlying disorders.

The abdominal CT scan and gallium scintigram revealed swollen lymph nodes of 1 cm in diameter, which disappeared spontaneously. Although concomitant swelling of abdominal lymph nodes were observed in patients with HSP,[4] the histological findings demonstrated that normal germinal centers were reduced and the majority of them were re-

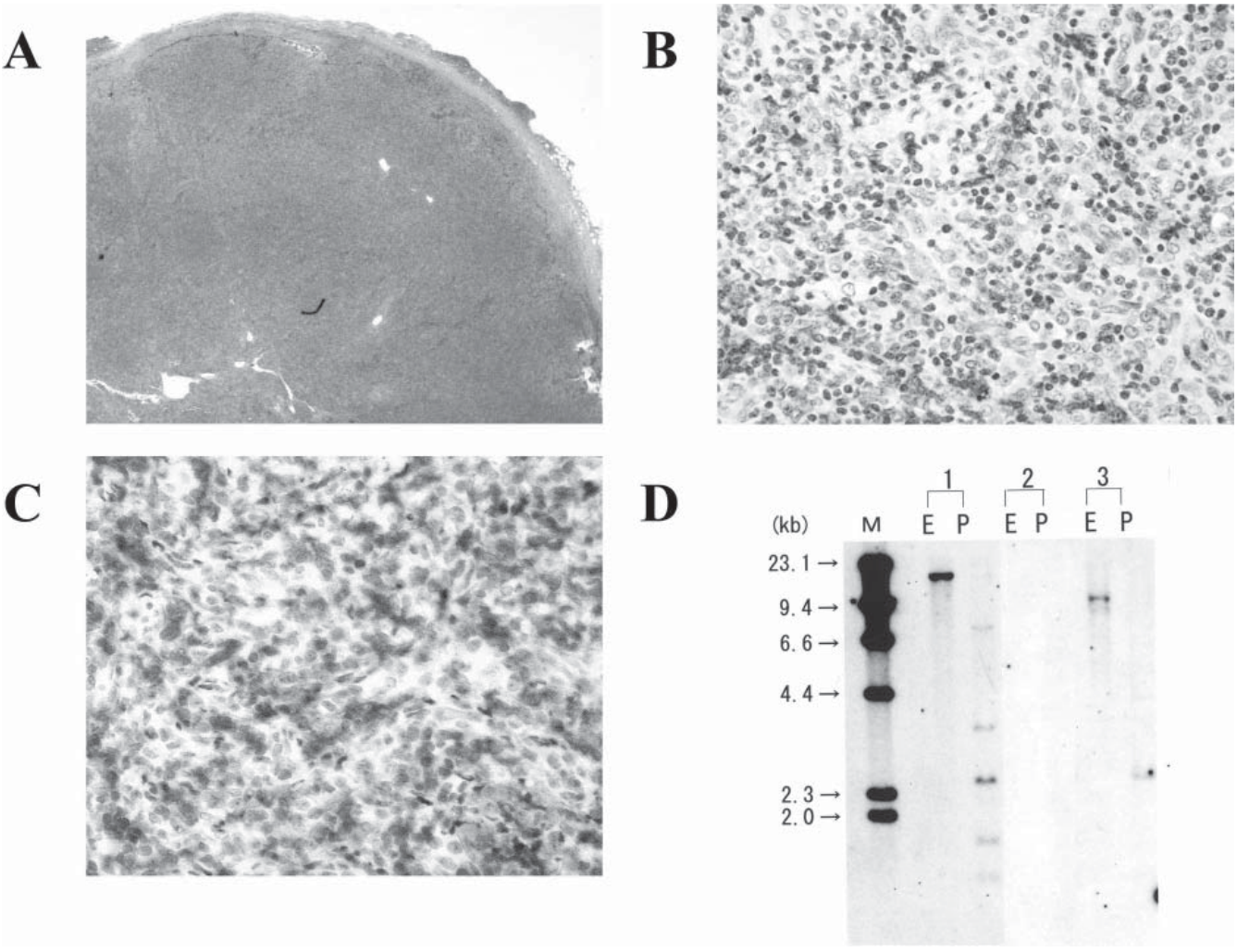

Fig. 3A–D. Lymph node biopsy. **A** In the histological studies, the lymph node was demonstrated to have the slightly fibrotic changes with normal structure of follicles. Small fraction of large lymphocytes with negative reactivity for L26 (**B**, ×200) and positive reactivity for CD3 (**C**, ×200) were detected in medullary sinus. **D** The monoclonal HTLV-I proviral integration in the lymph node was detected by Southern blotting. The samples were digested using *Eco*RI (*E*) or *Pst*I (*P*). *Lane 1*, positive control; *lane 2*, negative control; *lane 3*, sample from the patient; *lane M*, molecular weight marker

placed by aggregates of histiocytes and dendritic cells or granulomas.[5]

Gastrointestinal fiberscopic examination disclosed multiple ulcers in the stomach and *Helicobacter pylori*, but immunohistological studies revealed the infiltration of T cells into the gastric mucosa. Erosions and ulcers are usually observed in patients with HSP. However, they are sited mainly at the duodenum[6] rather than the stomach, and the accumulation of T cells is unusual. The presence of HTLV-I in our patient's serum was proved both by enzyme-linked immunosorbent assay and Western blotting. The correlation with *Helicobacter pylori* and gastric involvement of ATL has been previously reported.[7] It is possible that the lesions in the gastric mucosa in this case were caused by ATL invasion and the situation improved by the elimination of the bacteria. However, gastric involvement is unusual in the smoldering type, and mass forming, not the ulcerative lesions observed in this case, is most common in the lymphoma type. Unfortunately, the clonality of the invaded lymphocytes to the gastric mucosa could not be examined because of the small size of the biopsied specimen available to perform Southern blot analysis for HTLV-I proviral integration. On the other hand, the relationship between HSP and *Helicobacter pylori* infection has been demonstrated.[8,9] However, in this case the palpable purpura appeared only after the administration of the drugs for *Helicobacter pylori* infection, and was not ameliorated by the drugs.

The patients with ATL are classified into four clinical subtypes: smoldering, chronic, lymphoma, and acute types, according to the percentage of peripheral abnormal lymphocytes, total lymphocyte count, serum levels of calcium or LDH, and histologically proven lymphadenopathy.[10] Our patient could be classified into none of the four subtypes at his first admission: the peripheral lymphocyte number, lower than 4000, with more than 5% of abnormal lymphocytes; the level of LDH, more than 2-fold the upper normal range;

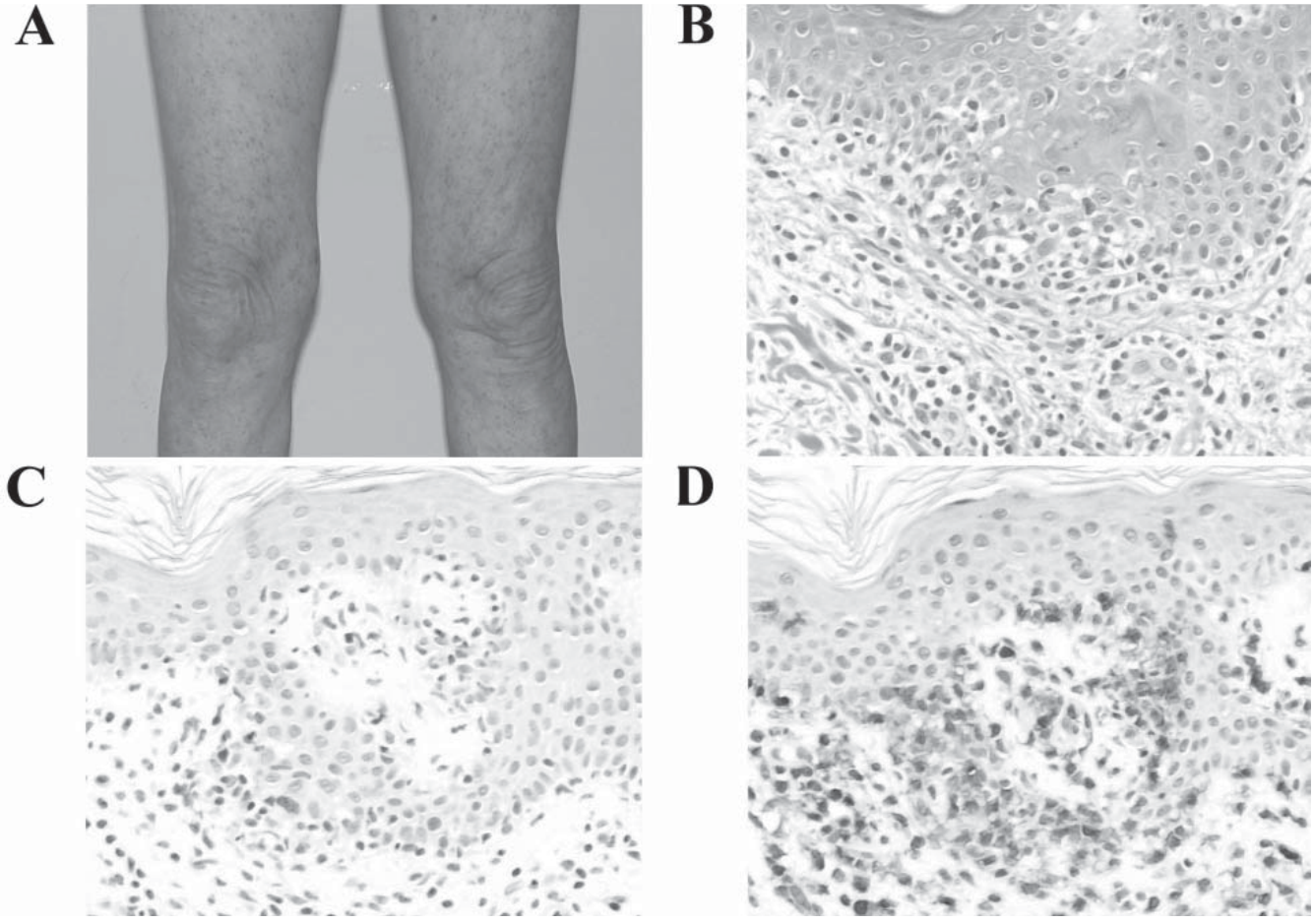

Fig. 4A–D. Skin lesions. **A** Multiple palpable purpura of 2–3 mm diameter appeared in bilateral lower extremities. **B** Histological examination revealed that small lymphocytes infiltrated to the basal cell layer of the skin (H&E staining, ×100), Many of them showed negative staining for L26 (**C**, ×100) and positive staining for UCHL-1 (**D**, ×100)

absence of lymphadenopathy that was histologically proven. Although the clinical course was consistent with HSP, we performed the biopsy of his small inguinal lymph node when his symptoms disappeared to determine how we should treat the patient. Histologically, the lymph node was not assessed as malignant lymphoma, containing small fractions of large-sized lymphocytes with T-cell phenotype. The monoclonal proviral integration of HTLV-I in the biopsied specimen was demonstrated by Southern blotting.[11] From this observation we could immediately perform chemotherapy when he suffered from symptoms caused by hypercalcemia with neither swelling of large-sized lymph nodes (typical for lymphoma type) nor increase of peripheral abnormal lymphocytes (typical for acute type).

Malignant neoplasms are occasionally associated with vasculitis. The prevalence of neoplasms in adults with cutaneous or systemic vasculitis has been reported to be 2.5%–5%.[12] Vasculitis is divided into cutaneous and systemic types, and HSP is classified into systemic vasculitis. Although vasculitis as paraneoplastic syndromes are more frequently associated with hematological malignancies than solid neoplasms, the majority of vasculitides associated with lymphoproliferative disorders is the cutaneous type.[13] There have been several reports about cutaneous vasculitis associated with hematological malignancies including T-cell lymphoma.[14–16] On the other hand, most (63%) of the malignant neoplasms associated with adult HSP were solid tumors, as reported by Pertuiset et al.[12] Many of hematologic malignancies that are associated with HSP are composed of B cells, such as Hodgkin's disease,[17,18] non-Hodgkin's B-cell lymphoma,[19,20] and multiple myeloma,[21–23] which may suggest a relationship of IgA increase in these diseases to the production of IgA containing immune complexes, which can cause vasculitis of small vessels in HSP.

HTLV-I is a retrovirus that is well known to be a cause of hematologic malignancy, adult T-cell lymphoma/leukemia.[24,25] It is also known to cause some chronic progressive diseases such as HTLV-I-associated myelopathy (HAM)[26–28] and HTLV-I-associated bronchopneumopathy (HAB).[29,30] Although it has also been reported that some vasculitides are accompanied by HTLV-I, containing uveitis and retinal vasculitis,[31–34] systemic vasculitis such as HSP has not been reported. In summary, this is a unique case of HTLV-I infection/ATL which mimics the clinical course of HSP, suggesting the importance of histological examinations in the diagnosis of HSP, particularly in adult patients.

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