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Case Report

A case of post-mogamulizumab relapse of acute-type adult T-cell leukemia/lymphoma successfully treated with mogamulizumab and etoposide

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Abstract: A 70-year-old man presented to us with the chief complaints of a generalized rash and a mass in the right clavicular region that he first noticed in the year 2012. Biopsy of the mass led to the diagnosis of cutaneous nodular mass-type adult T-cell leukemia/lymphoma (ATLL) in March 2013. Phototherapy was started, and the symptoms improved temporarily. However, in late June 2013, the serum lactate dehydrogenase (LDH) level increased to 358 IU/L, which was 1.6 times higher than the upper limit of the reference range; based on the findings, transformation of the disease to the acute type was diagnosed. The patient was treated with 6 courses of CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone), which resulted in complete remission (CR). However, the rash recurred in late October 2013, and treatment with mogamulizumab was initiated. A total of 8 courses of mogamulizumab were administered, which resulted in CR. The rash and cutaneous nodular masses recurred again in January 2014, and a total of 8 courses of mogamulizumab were administered again starting in February 2014. However, the patient's symptoms began to worsen gradually. Phototherapy was also initiated, but had to be discontinued due to the development of photosensitivity. Treatment with the combination of mogamulizumab and etoposide (25 mg/day for 21 days) was started in May 2014. The nodular mass rapidly decreased in size. The rash or cutaneous nodular mass had not recurred as of August 2014. Thus, combined therapy with mogamulizumab plus etoposide is considered to be effective for resolution of the cutaneous nodular masses in patients with ATLL.

Keywords: Adult T-cell leukemia/lymphoma, cutaneous nodular mass type, mogamulizumab, etoposide

Introduction

Combination chemotherapy has been used for acute-type and lymphoma-type adult T-cell leukemia/lymphoma (ATLL), but has not yielded satisfactory treatment outcomes, with a reported median survival time of 3 to 13 months [1-9]. On the other hand, allogeneic hematopoietic stem cell transplantation has been reported to be effective and is expected to improve prognosis [10-12]. However, patients who are not suitable candidates for transplantation have an extremely poor prognosis, and the standard of care for such patients needs to be established.

CC chemokine receptor 4 (CCR4) is expressed in the cancer cells in approximately 90% of patients with ATLL [13-15] and CCR4 positivity has been reported as an independent poor prognostic factor in patients with ATLL [13]. A humanized anti-CCR4 monoclonal antibody, mogamulizumab, specifically binds to CCR4 and exerts antitumor effect through antibody-dependent cell-mediated cytotoxicity (ADCC). Its effect is considered to be reduced in the nodular mass-type of ATLL with a small number of natural killer (NK) cells. A phase II clinical trial (0761-002 study) reported a response rate to mogamulizumab monotherapy of 50.0% (13/26 patients; complete remission (CR) in 30.8%;

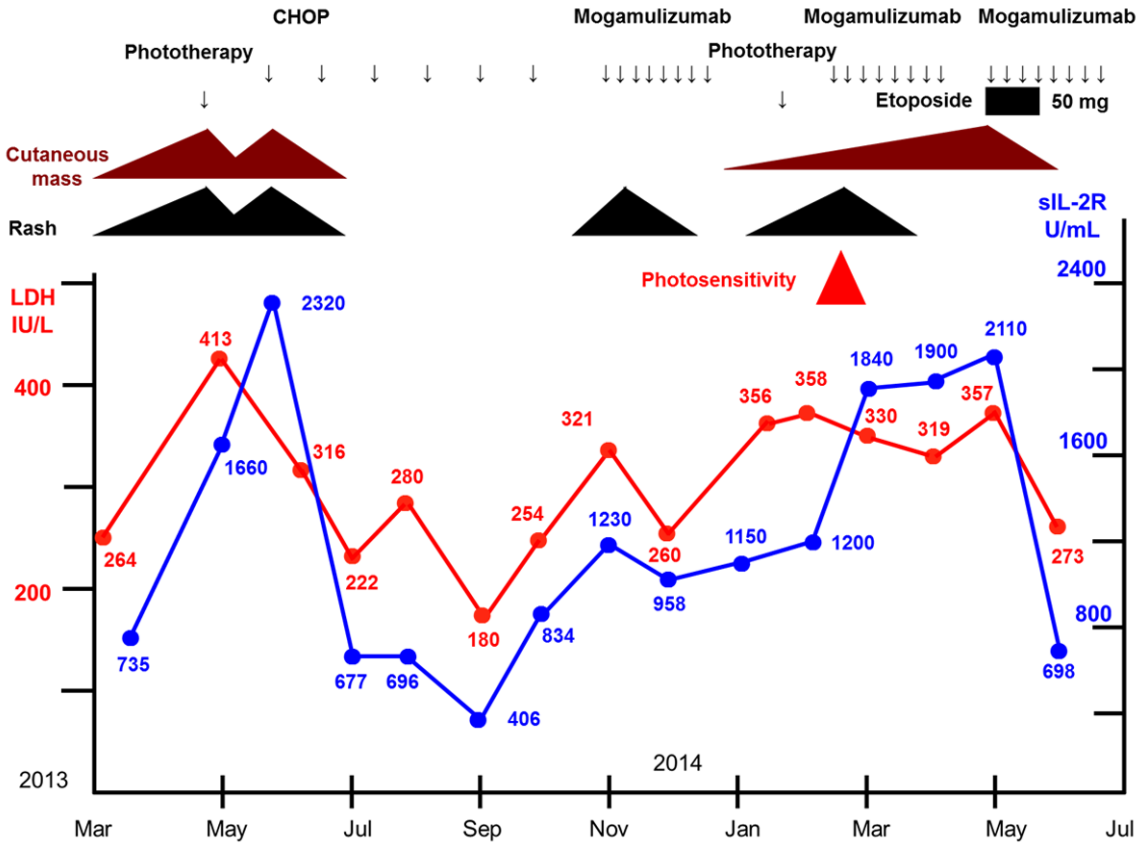
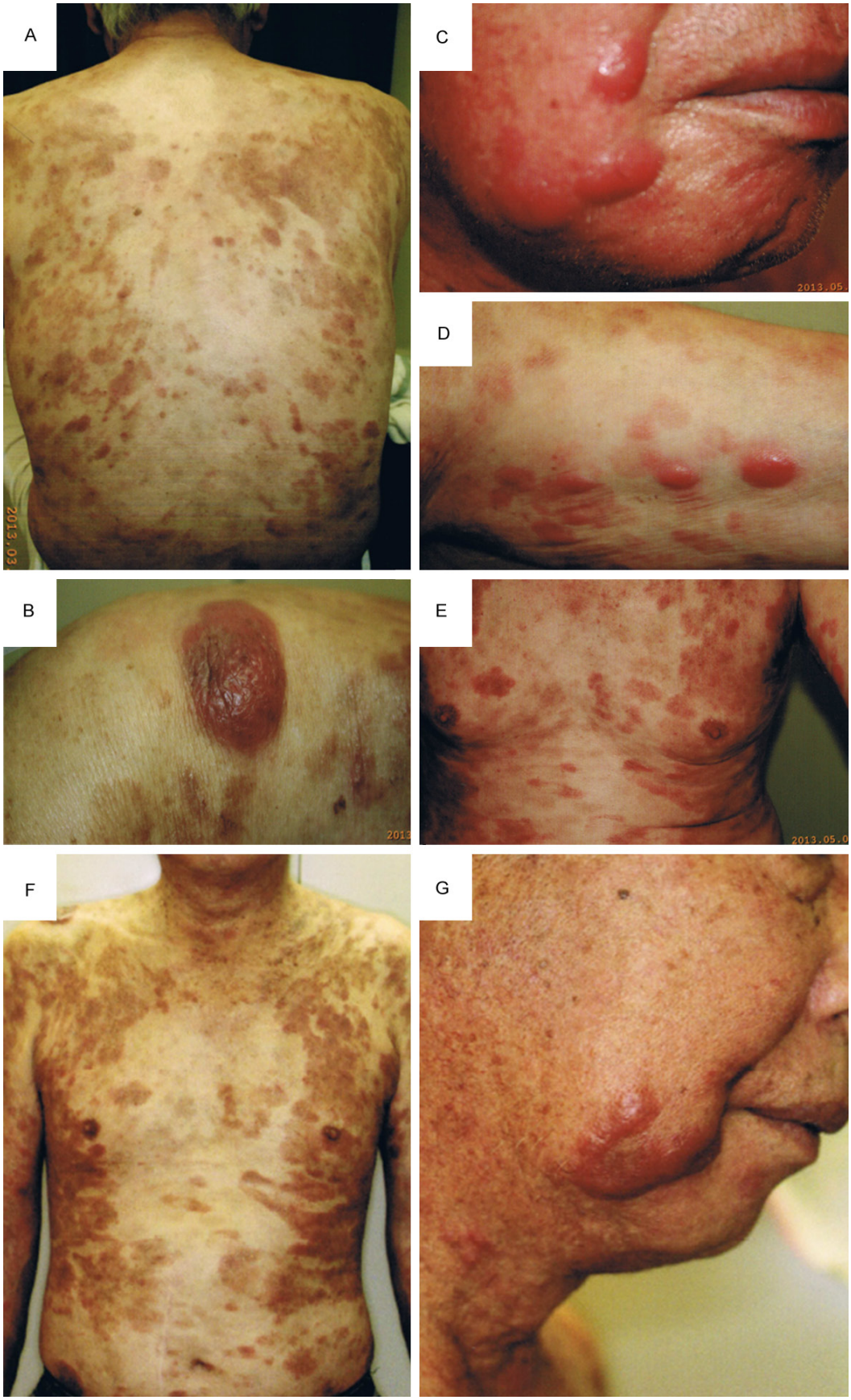


Figure 1. Clinical course. The patient visited the Department of Dermatology of our hospital with a generalized rash and a nodular mass in the right clavicular region in March 2013. Biopsy of the mass led to a diagnosis of cutaneous nodular mass-type ATLL. In May 2013, because new masses appeared and the rash worsened, phototherapy was started. The symptoms improved temporarily, however, transformation of the disease to the acute type was diagnosed in June 2013. CHOP therapy was started, and the rash and cutaneous nodular masses disappeared. In October 2013, the rash reappeared, and mogamulizumab therapy was started. Mogamulizumab therapy was completed in January 2014. However, new cutaneous nodular masses developed again, and mogamulizumab therapy was started again in February 2014. Phototherapy was additionally used, however, it had to be discontinued as the patient developed photosensitivity. The rash improved, but the cutaneous nodular masses enlarged even during treatment with mogamulizumab. Combined mogamulizumab plus etoposide therapy was started in May. The nodular masses decreased rapidly in size. The rash or cutaneous nodular masses had not recurred as of August 2014.

partial remission (PR) in 19.2%) in patients with CCR4-positive recurrent/relapsed ATLL (acute type, lymphoma type, or chronic type with poor prognostic factors of high blood urea nitrogen (BUN) levels, high serum lactate dehydrogenase (LDH) levels, and/or low serum albumin levels) after exclusion of treatment-resistant patients who had failed to achieve remission after previous chemotherapy. The incidence of adverse events was 100%, but the incidence of grade 3 to 4 adverse events was only approximately 15%, confirming the efficacy and tolerability of the drug [16]. However, the prognosis of ATLL after mogamulizumab monotherapy was not satisfactory, although better than that after conventional treatment [1-9], with a reported median progression-free survival (PFS) of 5.2 months and median overall survival (OS) of 13.7 months [16]. Therefore, we were prompted to investigate the efficacy of mogamulizumab administered in combination with other chemotherapies. However, the combination of mogamulizumab with other chemotherapies has not been reported yet, and the efficacy and tolerability of such combined treatment are still unknown. A clinical trial of combined therapy with mogamulizumab and LSG15 is currently in progress and its results are awaited. We encountered a patient with chemotherapy-resistant, multiple cutaneous nodular mass-type ATLL who was resistant to mogamulizumab monotherapy, but was successfully treated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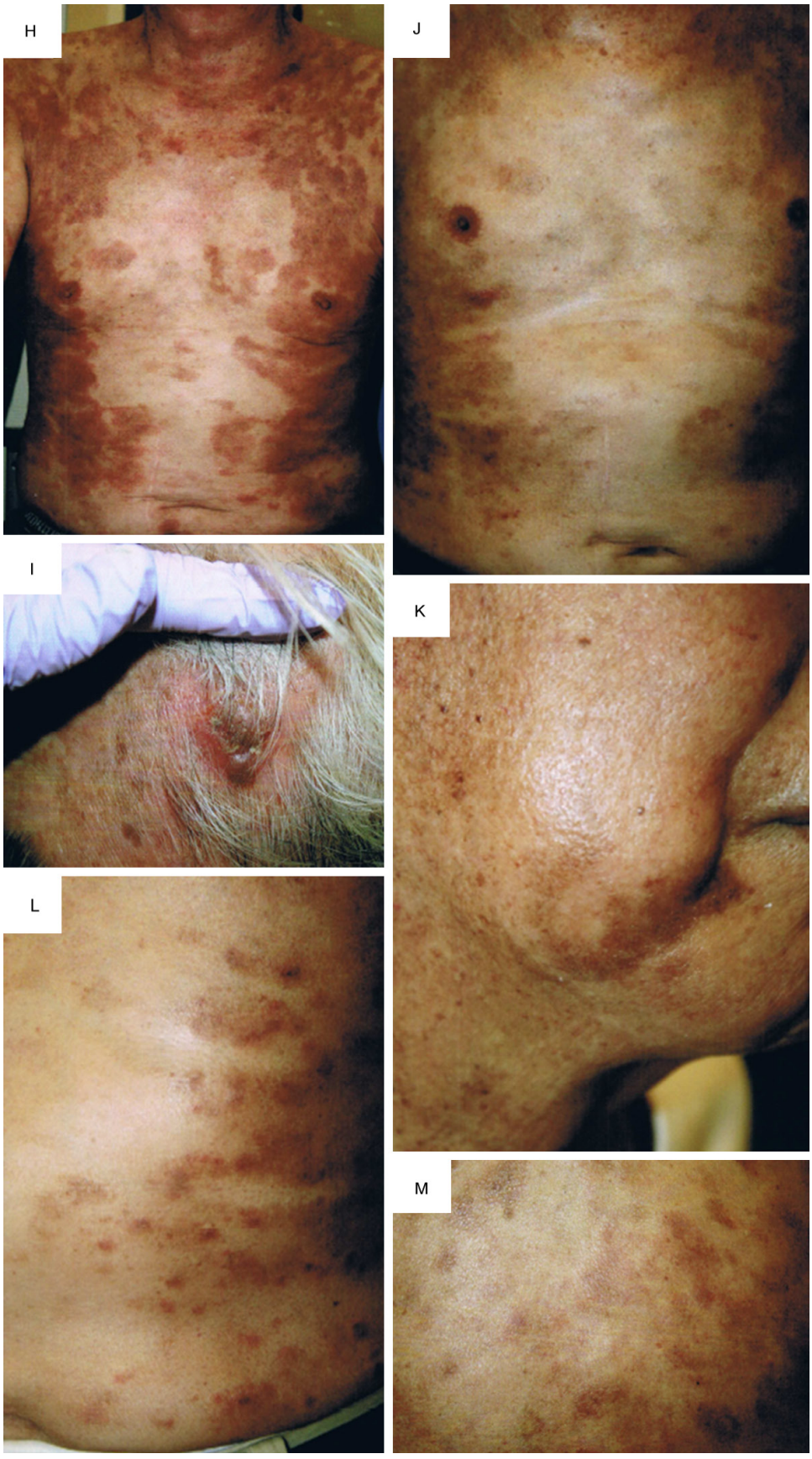
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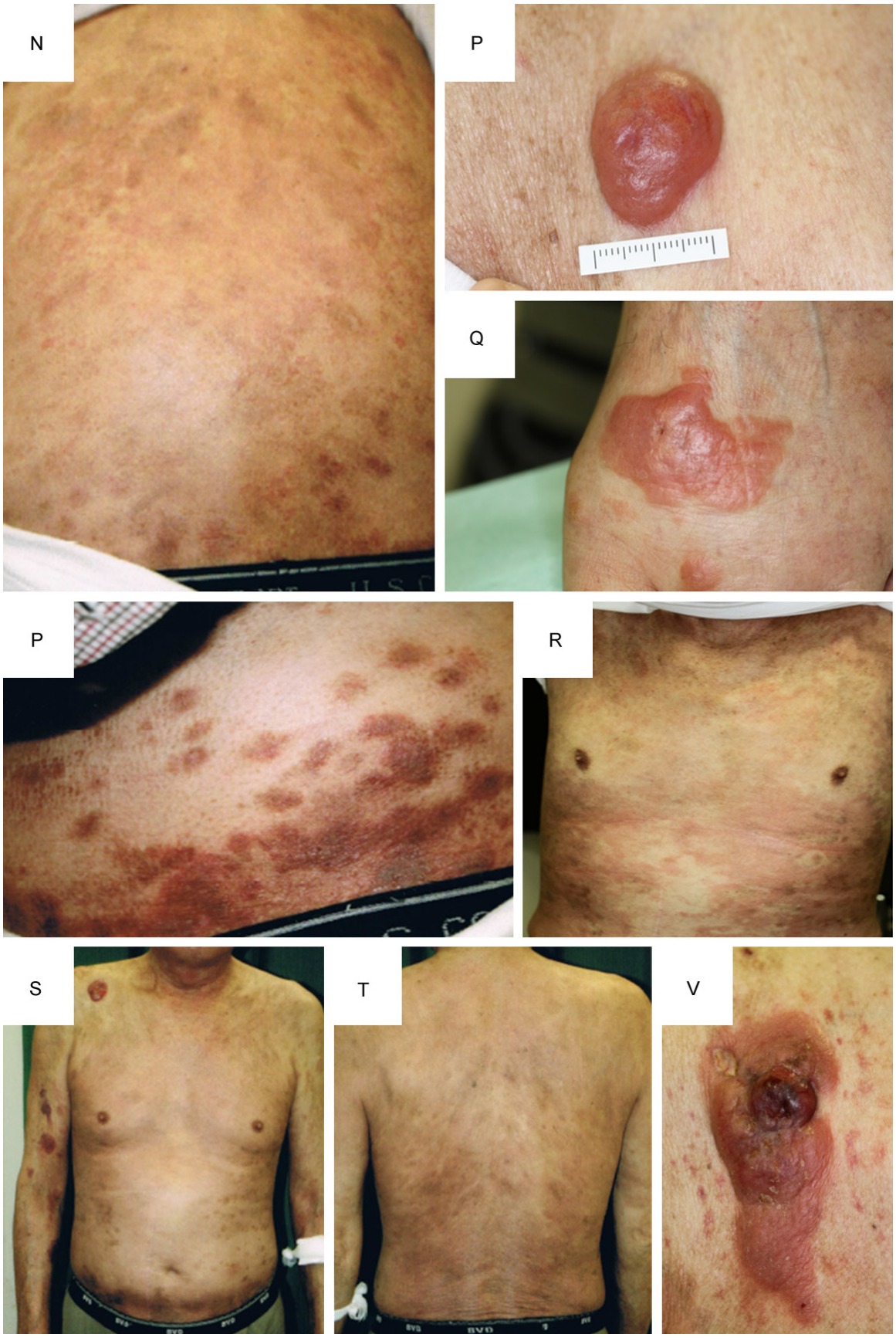
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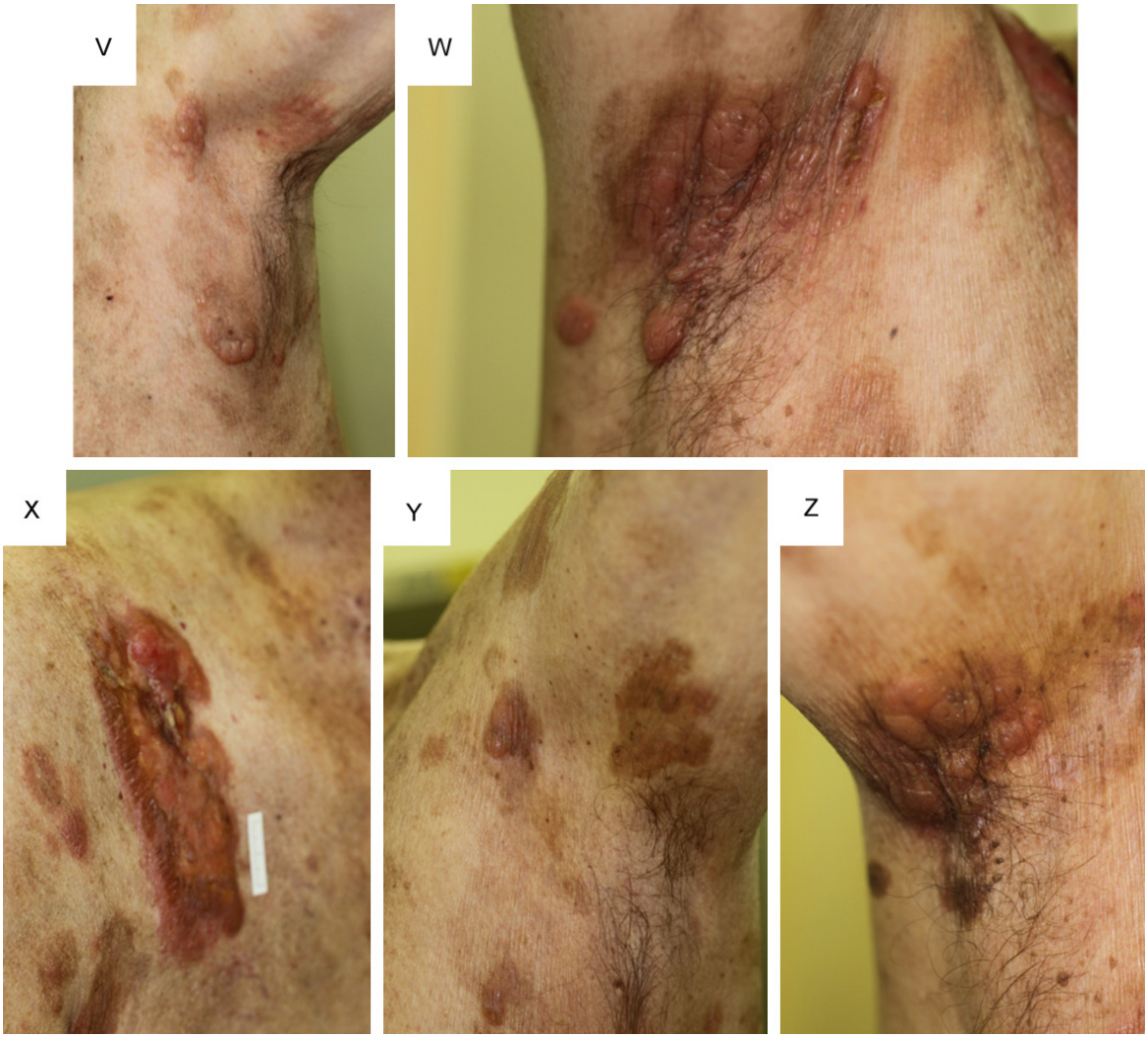

Figure 2. Cutaneous findings at the initial examination. A. Pigmented rash on the back. B. A flat, protruding mass measuring 4.5 cm in diameter was found in the right shoulder. C. New masses appeared in the right cheek. D. New masses appeared in the left axilla. E. The generalized rash worsened and pruritus developed. F. The generalized rash improved. G. The masses in the right cheek also temporarily decreased in size. H. The generalized rash worsened and pruritus developed. I. A new mass appeared in the head. J. The generalized rash improved. K. The masses in the right cheek disappeared. L. Rash and pruritus developed in the left abdomen. M. Rash and pruritus developed in the left abdomen. N. The rash and pruritus in the left abdomen improved. O. The rash and pruritus in the left abdomen improved. P. A mass measuring 2 cm in diameter appeared in the right clavicular region. Q. A mass measuring 3 × 2 cm in size appeared in the left instep. R. Generalized rash and pruritus developed. S. The generalized rash and pruritus improved. T. The generalized rash and pruritus improved. U. The mass in the right clavicular region increased in size. V. New masses appeared in the left axilla. W. New masses appeared in the right axilla. X. The mass in the right clavicular region decreased in size. Y. The masses in the left axilla decreased in size. Z. The masses in the right axilla decreased in size.

with mogamulizumab administered in combination with etoposide, without any serious adverse events. This is the first report of the efficacy and tolerability of combined mogamulizumab plus etoposide therapy, suggesting that this combination therapy may be a valid treatment option for patients with ATLL who are not suitable candidates for stem cell transplantation.

Case report

A 70-year-old man, who came from Nagasaki, presented to us with the chief complaints of a generalized rash and a mass in the right clavicular region. His medical history included hypertension; however, there was no significant family history. He first noticed a generalized rash over the body in the year 2012. He

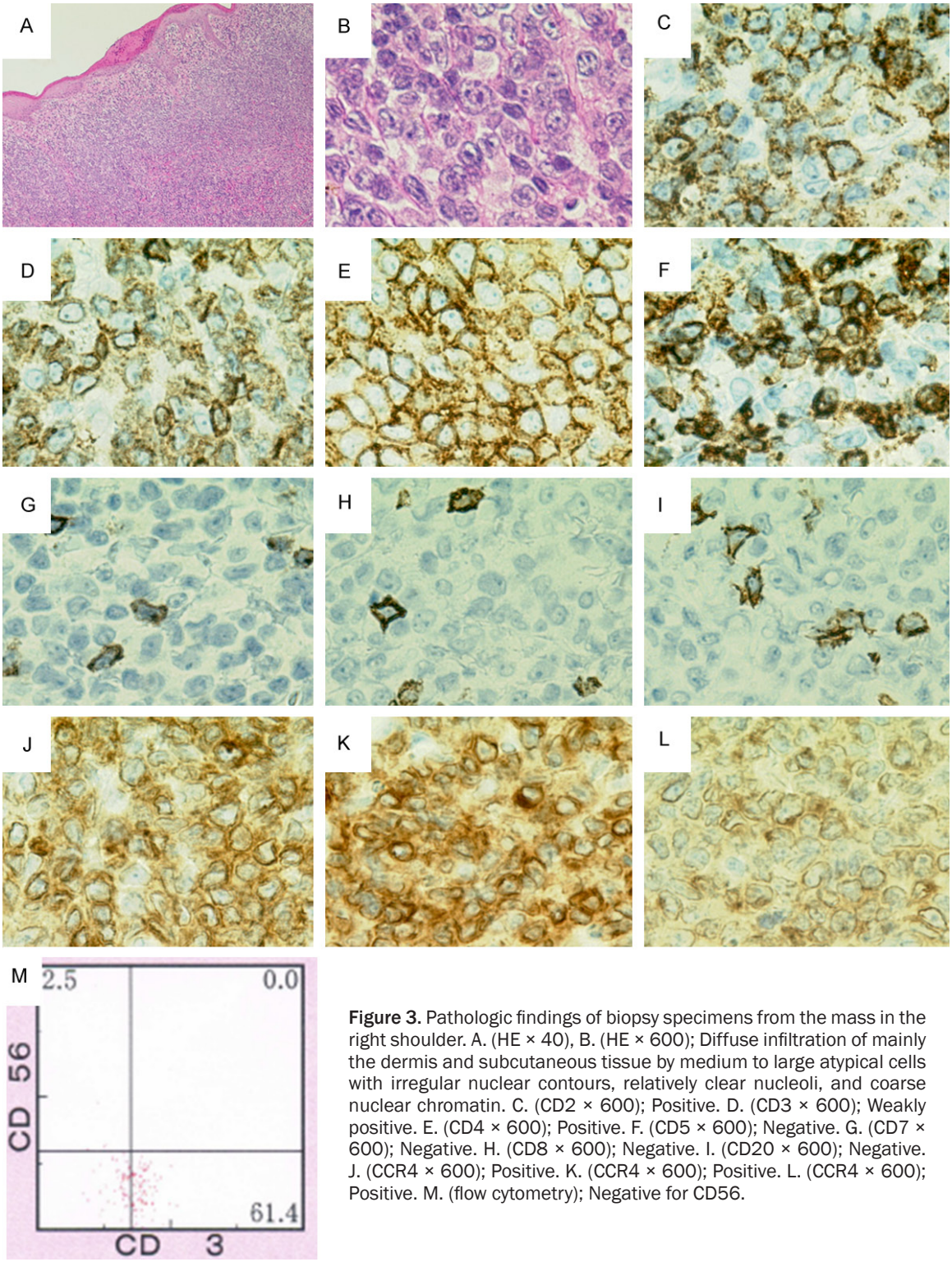

Figure 3. Pathologic findings of biopsy specimens from the mass in the right shoulder. A. (HE × 40), B. (HE × 600); Diffuse infiltration of mainly the dermis and subcutaneous tissue by medium to large atypical cells with irregular nuclear contours, relatively clear nucleoli, and coarse nuclear chromatin. C. (CD2 × 600); Positive. D. (CD3 × 600); Weakly positive. E. (CD4 × 600); Positive. F. (CD5 × 600); Negative. G. (CD7 × 600); Negative. H. (CD8 × 600); Negative. I. (CD20 × 600); Negative. J. (CCR4 × 600); Positive. K. (CCR4 × 600); Positive. L. (CCR4 × 600); Positive. M. (flow cytometry); Negative for CD56.

received topical steroid therapy and antiallergic drugs at a local hospital, however, the symptoms did not improve and he visited the Department of Dermatology of our hospital in March 2013 (see **Figure 1** for the clinical course). He had a generalized pigmented rash over the body and a flat, protruding mass in the right clavicular region measuring 4.5 cm in

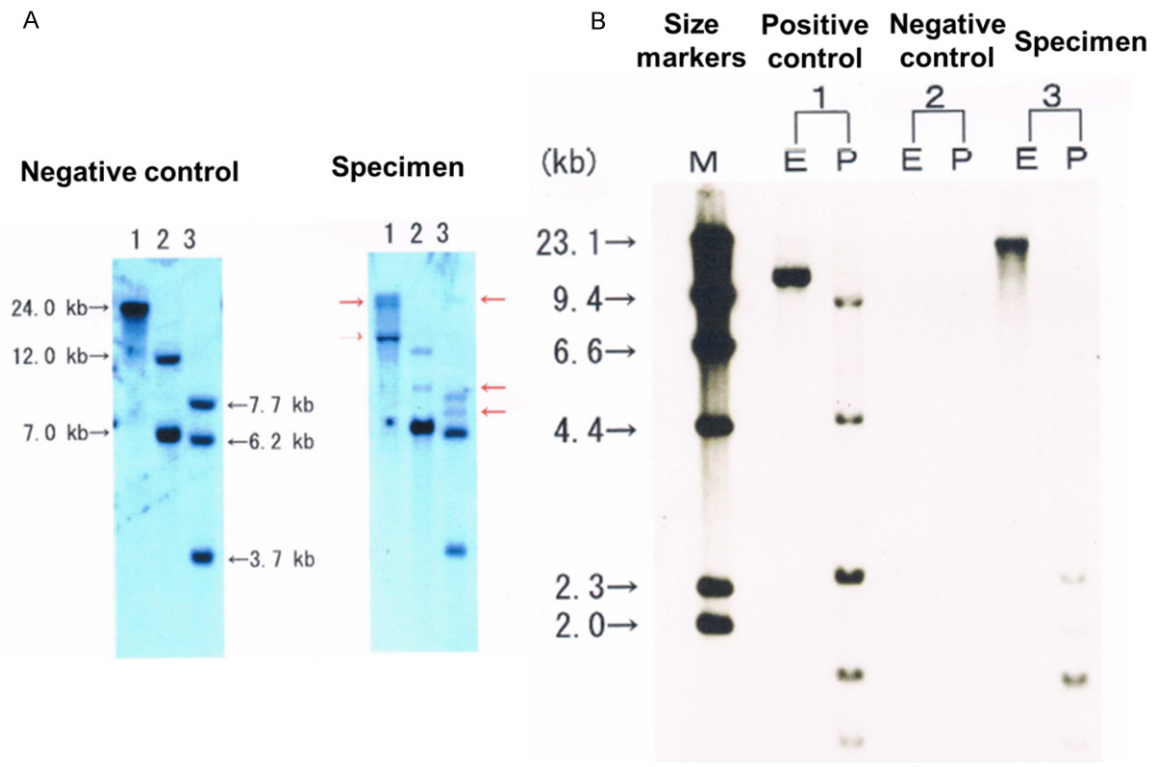

Figure 4. A. Southern blot assay (TCRCβ1). The restriction enzymes used were lane 1, BamH I; lane 2, EcoR V; lane 3, Hind III. Red arrows show the rearranged bands. B. Southern blot assay (HTLV-1 DNA). The restriction enzymes used were: E, EcoRI digestion; P, PstI digestion. HTLV-1 provirus was detected in lane 3 (specimen).

diameter (**Figure 2A**, **2B**). There was no superficial lymphadenopathy or hepatosplenomegaly. A positive test result was obtained for serum human T-cell leukemia virus-1 (HTLV-1) antibodies (particle agglutination (PA) method) (titer 1:1024; reference value £ 1:16), raising the suspicion of ATLL, and the patient was referred to our department. Southern blot analysis of peripheral blood did not reveal any HTLV-1 provirus (data not shown). Hematoxylin-eosin (HE) staining of biopsy specimens from the mass in the right shoulder showed diffuse infiltration of mainly the dermis and subcutaneous tissue, and occasionally the epidermis, by medium to large atypical cells with irregular nuclear contours, relatively clear nucleoli, and coarse nuclear chromatin (**Figure 3A**, **3B**). The cells were positive for cluster of differentiation (CD) 2 and CD4 (**Figure 3C**, **3E**), weakly positive for CD3 (**Figure 3D**), and negative for CD5, CD7, CD8, CD20 and CD56 (**Figure 3F-I**, **3M**). CCR4 expression was positive (**Figure 3J**). Southern blot analysis revealed positive results for T-cell receptor β-1 rearrangement (TCRCβ1) and HTLV-1 provirus (**Figure 4A**, **4B**). From the findings, the patient was diagnosed as having ATLL. G-banded chromosomes could not be identified due to poor growth (data not shown).

The laboratory findings are shown in **Table 1**. Serum levels of LDH and soluble interleukin-2 receptor (sIL-2R) were elevated to 264 IU/L and 735U/mL, respectively. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) showed FDG accumulation (SUVmax 6.0) only in the area of the mass in the right shoulder (**Figure 5A**, **5B**). Bone marrow examination revealed no infiltration of ATLL cells, and Southern blot analysis showed negative results for HTLV-1 provirus and TCRCβ1 (data not shown). Based on the above, the patient was diagnosed as having cutaneous mass-type ATLL. Because new masses appeared in the right cheek and left axilla (**Figure 2C**, **2D**) and the generalized rash (**Figure 2E**) and pruritus also worsened in May, phototherapy was started. The generalized rash and cutaneous mass in the cheek improved temporarily (**Figure 2F**, **2G**), however, the rash worsened again (**Figure 2H**) and a new mass appeared in

Table 1. Laboratory findings

Peripheral blood	WBC	6,000/μL
	Neut	76.7% ↑
	Ly	12.3% ↓
	Mono	7.8% ↑
	Eo	1.3%
	Ba	0.2%
	RBC	375 × 10^4/μL ↓
	Hb	12.9 g/dL ↓
	Ht	40.5%
	MCV	107.8 fl ↑
	MCH	34.3 pg
	Plt	20.3 × 10^4/μL
	Reti	1.5%
Blood coagulation profile	PT	[3] 100%
	APTT	22.8 sec
Urinalysis	No abnormalities	
Immuno-serological findings	IgG	1075 mg/dL
	IgA	206 mg/dL
	IgM	46 mg/dL ↓
	Serum β2MG	1.9 mg/dL ↑
	sIL-2R	735 U/mL ↑
Biochemistry	T.P	6.0 g/dL ↓
	Alb	3.4 g/dL ↓
	AST	24 IU/L
	ALT	21 IU/L
	LDH	264 IU/L ↑
	ALP	243 IU/L
	γ-GTP	124 IU/L ↑
	T-Bil	0.8 mg/dL
	BUN	26 mg/dL ↑
	Cr	1.02 mg/dL
	Uric acid	7.2 mg/dL ↑
	Corrected Ca	8.8 mg/dL
	CRP	0.3 mg/dL
	Ferritin	158.8 ng/mL
Biopsy of the mass in the right shoulder	Chromosome (G-banding)	Poor growth
	IgHJH (Southern blot analysis)	Negative
	TCRCβ1 (Southern blot analysis)	Positive ↑
	HTLV-I DNA (Southern blot analysis)	HTLV-I provirus detectable ↑
Flow cytometry of biopsy specimens from the mass in the right shoulder	CD1	4.8%
	CD2	91.7% ↑
	CD3	61.4% ↑
	cyCD3	91.5% ↑
	CD4	95.0% ↑
	CD5	29.4%
	CD7	5.3%
	CD8	2.1%
	TCR-αβ	12.7%
	TCR-γδ	0.7%
	CD10	5.9%
	CD19	1.1%
	CD20	12.0%
	CD22	3.9%
	κ	12.8%
	λ	6.4%

CD13	6.3%
CD25	66.3% ↑
CD30	5.0%
CD34	1.2%
CD45	99.2% ↑
CD56	2.5%
HLA-DR	40.7%
TdT	6.5%

WBC, white blood cell; Neut, neutrophil; Ly, lymphocyte; Mono, monocyte; Eo, eosinophil; Ba, basophil; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Plt, platelet; Reti, reticulocyte; PT, prothrombin activity; APTT, activated partial thromboplastin time; IgG, serum immunoglobulin G; IgA, serum immunoglobulin A; IgM, serum immunoglobulin M; β2MG, serum β2 microglobulin; T.P, serum total protein; Alb, serum albumin; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; ALP, serum alkaline phosphatase; γ-GTP, serum γ-guanosine triphosphate glutamyl transpeptidase; T-Bil, serum total bilirubin; Cr, serum creatinine; Ca, serum calcium; CRP, serum C-reactive protein; IgHJH, immunoglobulin heavy chain rearrangement; cy, cytoplasmic; HLA-DR, human leukocyte antigen-DR; TdT, TdT activity.

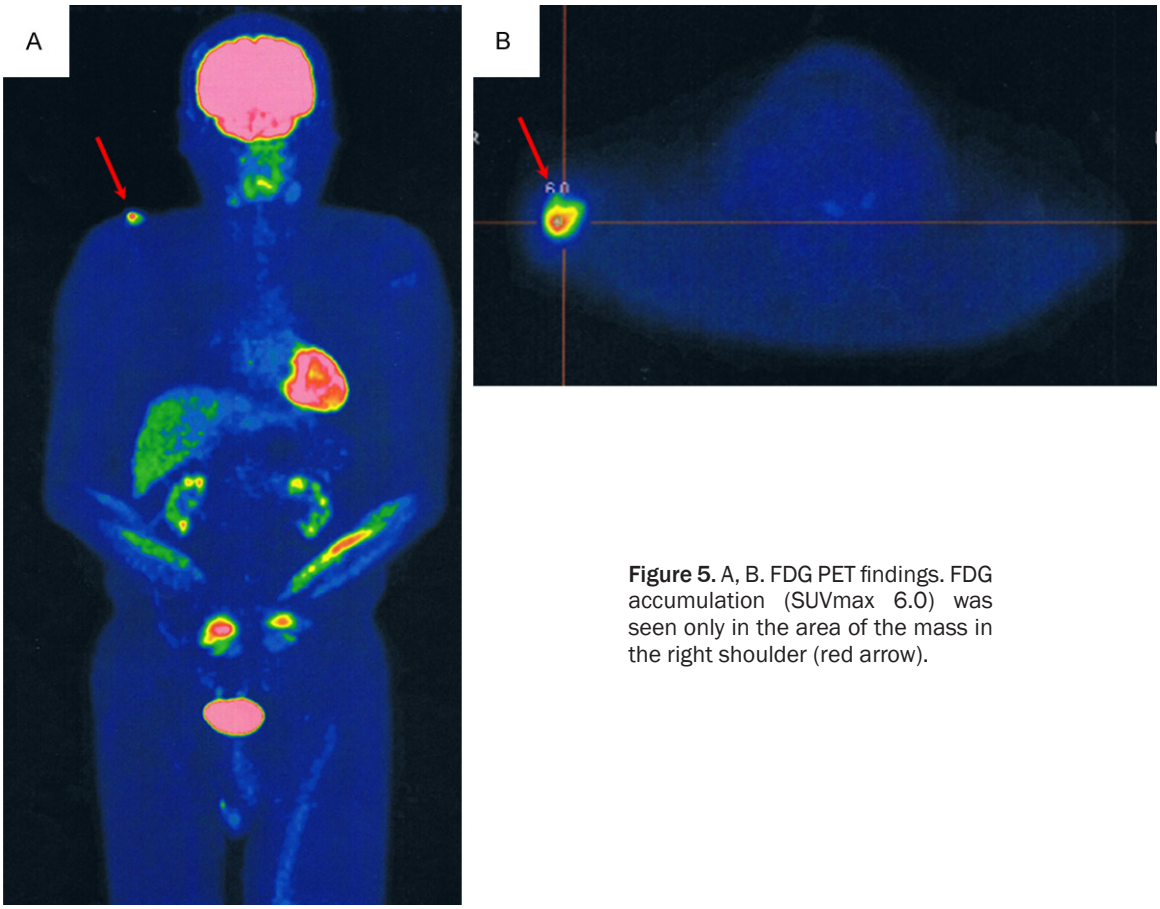

Figure 5. A, B. FDG PET findings. FDG accumulation (SUVmax 6.0) was seen only in the area of the mass in the right shoulder (red arrow).

the head (**Figure 2I**). In late June, the serum LDH level increased to 358 IU/L (reference range, 119 to 229 IU/L), 1.6 times higher than the upper limit of the reference range, leading to a diagnosis of transformation of the disease to the acute type. CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) was started, and the generalized rash, pruritus and cutaneous masses disappeared (**Figure 2J**, **2K**). A total of 6 courses of CHOP were administered, and the treatment was completed in early October 2013. However, rash and pruritus developed in the left abdomen in late October 2013 (**Figure 2L**, **2M**). Mogamulizumab therapy (a total of 8 weekly doses of 1 mg/kg of mogamulizumab) was started in early November. The rash and pruritus improved (**Figure 2N**, **2O**), and the treatment was completed in early January 2014. However, a mass measuring 2 cm in diameter developed in the right clavicular region (**Figure 2P**) and another measuring 3 × 2 cm in size in

the left instep (**Figure 2Q**) in late January 2014. The generalized rash and pruritus (**Figure 2R**) recurred again in early February. Biopsy of the mass in the right clavicular region confirmed CCR4 positivity again (**Figure 3K**), and mogamulizumab treatment (a total of 8 weekly doses of 1 mg/kg of mogamulizumab) was started again in late February. Phototherapy was also used; however, it was discontinued as the patient developed photosensitivity. The rash and pruritus improved (**Figure 2S**, **2T**), and the mogamulizumab treatment was completed in mid-April. However, even during the treatment, the mass in the right clavicular region enlarged in size (**Figure 2U**), and new masses developed in the left and right axillae (**Figure 2V**, **2W**). The rash and pruritus recurred again in early May 2014. Biopsy of the mass in the right clavicular region again confirmed CCR4 positivity (**Figure 3L**). Because mogamulizumab monotherapy was not effective for the masses and the rash and pruritus recurred immediately after the completion of treatment, combination therapy with mogamulizumab (a total of 8 weekly doses of 1 mg/kg of mogamulizumab) plus etoposide (25 mg/day of etoposide for 21 days) was started in early May. The rash and pruritus disappeared and the masses in the right clavicular region and left and right axillae also rapidly decreased in size (**Figure 2X-Z**). The rash and cutaneous masses had not recurred as of August 2014.

Discussion

This is the first case report of administration of a total of 24 doses of mogamulizumab. In addition, although these doses were given within a short period of time (approximately 8 months) after the first dose, the treatment was safe, with no adverse events.

Mogamulizumab monotherapy was effective for the rash, but not sufficiently effective for the cutaneous nodular masses. However, the combination of mogamulizumab plus etoposide was effective for the cutaneous nodular masses. Treatment with this combination was safe, with no adverse events. This is also the first reported case of use of mogamulizumab in combination with etoposide.

In this case, the tumor mass cells were negative for CD56 (**Figure 3M**), suggesting that NK cells were absent and that ADCC activity was not induced, and this was speculated to be responsible for the insufficient efficacy of mogamulizumab monotherapy against the cutaneous nodular masses. Actually, it is speculated that the degree of ADCC activity of the NK cells and monocytes/macrophages may have an influence on the success of the treatment [16]. Additional use of etoposide is considered to be useful for the nodular mass-type in which the number of NK-T cells is small and ADCC is not expected to be very high, as in this case. In addition, it has been suggested that the antitumor effect of mogamulizumab is exerted not only through ADCC, but also by enhancement of the tumor immunity via inhibition of regulatory T (T reg) cells [17, 18]. It is necessary to compare and investigate CD56-positive regions with residual NK-T cells and CD56-negative regions with no residual NK-T cells in the tumors. Furthermore, a late responder to mogamulizumab monotherapy has also been reported [19], and it is necessary to investigate how long it would take to achieve efficacy with mogamulizumab monotherapy in the future.

The additional use of phototherapy during treatment with mogamulizumab may cause photosensitivity, as in this case, and it is important to bear this in mind.

When mogamulizumab monotherapy was administered to this patient for the first time, 8 courses were given. However, the rash recurred and cutaneous nodular masses appeared within a short period of time, i.e., 2 weeks after completion of treatment, suggesting that CR was not achieved and that the residual lesions led to recurrence. Therefore, if CCR4 positivity is detected after treatment with mogamulizumab, it is necessary not to discontinue the treatment after 8 courses, and to further continue the treatment until CCR4 expression becomes negative (CR is achieved).

Johno et al. classified cutaneous-type ATLL into the erythematous popular- and nodular mass-types [20]. The cutaneous erythematous popular-type is often treated with topical steroids, ultraviolet irradiation, electron beam irradiation, interferon and others [21]. The localized cutaneous nodular mass-type is treated with electron beam therapy or by surgical resection, and the extensive cutaneous nodular mass-type is treated in a similar way to the chronic-

and lymphoma-types [21]. The prognosis of the cutaneous nodular mass-type is poor, with a reported median survival time of approximately 26 months [20]. In addition, the localized-type shows a relatively long course without visceral lesions (a little over 1 year), whereas the extensive type has a short course without visceral lesions (a little over 6 months), indicating a poorer prognosis of the extensive type [20]. The present patient had the extensive type of disease, with an expected extremely poor prognosis. Allogeneic hematopoietic stem cell transplantation has been reported to be effective for ATLL [10-12], and allogeneic hematopoietic stem cell transplantation is considered to be indicated for the extensive cutaneous nodular mass-type, that has a particularly poor prognosis. However, it is considered that combined mogamulizumab plus etoposide therapy may be a treatment option for elderly patients with the cutaneous nodular mass-type, who are not suitable candidates for allogeneic hematopoietic stem cell transplantation, like the present case.

It has been reported that the appearance of skin disorders due to mogamulizumab is associated with an improved prognosis [22]. The present patient had no skin disorders caused by mogamulizumab, suggesting a poor prognosis. Careful follow-up is necessary.

Disclosure of conflict of interest

None.

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