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Case Report

Peripheral T cell lymphoma, not otherwise specified with myelofibrosis: report of a case with review of the literature

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Abstract: A 68-year-old man presented to us with pancytopenia, erythroderma, and multiple lymphadenopathies. Lymph node biopsy led to the diagnosis of peripheral T-Cell lymphoma-not otherwise specified (PTCL-NOS). Immunostaining of the lymph node biopsy specimens for cytokines revealed that the tumor cells were positive for plated-derived growth factor (PDGF), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), interleukin-2 (IL-2), and transforming growth factor-β (TGF-β). Bone marrow biopsy revealed infiltration by the PTCL-NOS and myelofibrosis (MF). Bone marrow blood was negative for JAK-2V617F. Bone marrow immunostaining for cytokines showed that the tumor cells were positive for PDGF, b-FGF, VEGF, TNF-α, IFN-γ, IL-1β, IL-2, and TGF-β. The patient was initiated on treatment, and after the first course of CHOP therapy, the bone marrow infiltration by the PTCL-NOS and MF improved. Repeat immunostaining of bone marrow biopsy specimens for cytokines showed that the tumor cells had become negative for PDGF, VEGF, TNF-α and TGF-β. However, after the second course of CHOP therapy, the bone marrow infiltration by the PTCL-NOS and MF worsened. Immunostaining of bone marrow specimens for cytokines again revealed positive staining results of the tumor cells for PDGF, TNF-α, and TGF-β. At the completion of the first course of treatment, the infiltration by the PTCL-NOS improved, but not the pancytopenia.

Keywords: Peripheral T-Cell lymphoma-not otherwise specified (PTCL-NOS), bone marrow fibrosis (MF), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNFα), transforming growth factor-β (TGF-β)

Introduction

Primary myelofibrosis (MF) is characterized by clonal proliferation of megakaryocytes, monocytes and histiocytes, and the various cytokines produced by these cells, such as transforming growth factor-β (TGF-β), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF) and tumor necrosis factor α (TNF-α), are thought to be among the major causes of MF [1-3]. Malignant lymphoma complicated by MF is rare and the cause of MF in this condition remains unknown in many cases [4-12]. However, some studies, including our previous study, have speculated that cytokines such as TGF-β [13-15], b-FGF [2, 16] and platelet-derived growth factor (PDGF) [2, 14, 15], may be responsible for the MF associated with malignant lymphoma, just as in the case of primary MF.

This is the first reported case of T-cell lymphoma complicated by MF, in which both immunostaining and serum assays were performed for cytokines. In the patient presented here, while on immunohistochemistry, the tumor cells showed positive staining for PDGF, TGF-β and TNF-α, serum assay revealed elevation only of the serum titers of TNFα, suggesting that the tumor cells in the bone marrow produced PDGF, TGF-β, and TNF-α, thereby causing MF. This is the first report of TNF-α production in the bone

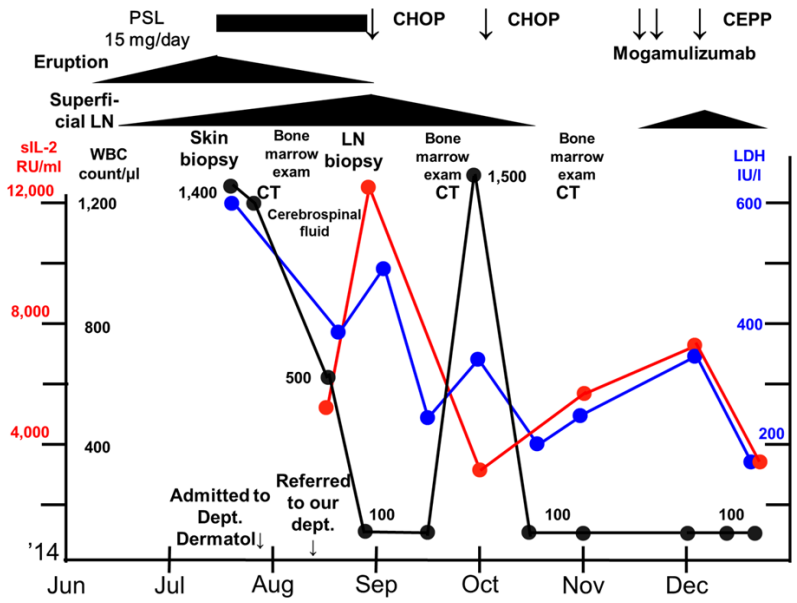

Figure 1. Clinical course. PSL: prednisolone; CHOP; cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone; CEPP: cyclophosphamide hydrate, etoposide, prednisolone, and procarbazine hydrochloride; WBC: white blood cell; LDH, lactate dehydrogenase.

marrow in a patient with T-cell lymphoma and MF.

Case

A 68-year-old man was referred to us with pancytopenia, generalized edema and erythroderma, and multiple superficial and deep lymphadenopathies. He had no significant past medical or family history. His clinical course is shown in **Figure 1**. In early June 2014, he visited a local hospital with generalized edema and erythroderma. He was prescribed a topical steroid, but showed no improvement. In early July, he developed pancytopenia, and in late July, he was admitted to the Department of Dermatology of our hospital. Skin biopsy led to the diagnosis of erythrodermic psoriasis. Treatment with prednisolone 15 mg/day was started, and the generalized edema and erythroderma improved. However, the pancytopenia worsened and a whole-body CT showed multiple superficial and deep lymphadenopathies (**Figure 2A-D**). Therefore, the patient was referred to our department in mid-August.

The findings at the time of admission were as follows: height 173.1 cm, weight 71.0 kg, body temperature 37.4°C, blood pressure 128/62 mm Hg, pulse 80/minute, regular, clear consciousness, pallor of the palpebral conjunctiva, no icterus of the bulbar conjunctiva, no palpable liver or spleen, and no abnormal neurological findings. A few, elastic soft, superficial lymph nodes measuring about 3 cm in size were palpable in both the axillae and both inguinal regions. Mild eruption with pigmentation was seen over the entire body.

The laboratory findings on admission are shown in **Table 1**. He had pancytopenia and elevated serum levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP). In addition, the soluble IL-2 receptor (sIL-2R) level was as high as 5,410 U/mL. Among the serum cytokines, only the serum level of tumor necrosis factor α (TNF-α) was elevated.

The patient's clinical course after referral to our department is shown in **Figure 1**. First, a left axillary lymph node biopsy was performed; examination of hematoxylin and eosin (HE)-stained sections showed that the basic architecture of the lymph node was lost, with proliferation of medium-sized atypical cells with irregular nuclear contours (**Figure 3A**, **3B**). Immunostaining revealed that the tumor cells were positive for CD2, CD3, and C-C chemokine receptor type 4 (CCR4) (**Figure 3C**, **3D**, **3P**) and negative for CD4, CD5, CD7, CD8, CD10, CD20, CD56, Epstein-Barr virus-encoded small RNA (EBER), granzyme B, and programmed cell death 1 (PD1) (**Figure 3E-J**, **3L-O**); CD21 immunostaining showed no proliferation of follicular dendritic cells (**Figure 3K**). G-banding chromosome analysis of the lymph nodes revealed a complex karyotype (**Table 1**), and Southern blot analysis showed rearrangement of T-Cell Receptor Cβ1 (TCRCβ1) (data not shown). Based on the above findings, the patient was diagnosed as having peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS). Furthermore, immunostaining for cytokines revealed that the tumor cells in the lymph nodes were positive for PDGF, b-FGF, VEGF,

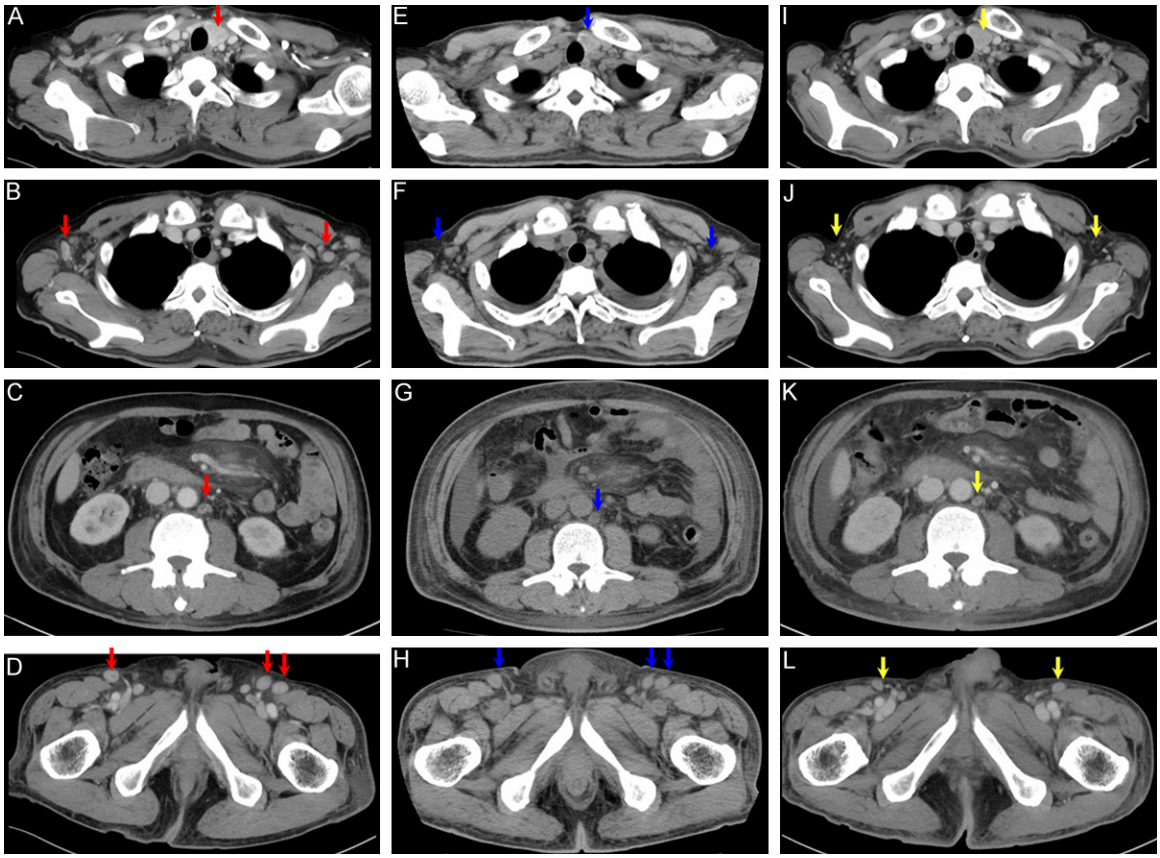

Figure 2. CT findings. A-D. Before CHOP therapy. E-H. After one course of CHOP therapy. I-L. After two courses of CHOP therapy. A. A low-density mass is seen in the left lobe of the thyroid gland (red arrow); B. Enlarged lymph nodes are seen in both the axillae (red arrows); C. Enlarged lymph nodes are seen around the aorta (red arrow); D. Enlarged lymph nodes are seen in both inguinal regions (red arrows); E. Decrease in the size of the low-density mass in the left lobe of the thyroid gland (blue arrow); F. Decrease in the size of the lymph nodes in both the axillae (blue arrows); G. Decrease in the size of the lymph nodes around the aorta (blue arrow); H. Decrease in the size of the lymph nodes in both inguinal regions (blue arrows); I. The low-density mass in the left lobe of the thyroid gland remains unchanged in size (yellow arrow); J. Further decrease in the size of the lymph nodes in both the axillae (yellow arrows); K. Further decrease in the size of the lymph nodes around the aorta (yellow arrow); L. Further decrease in the size of the lymph nodes in both inguinal regions (yellow arrows).

TNF-α, IFN-γ, IL-1β, IL-2, and TGF-β (**Figure 4A-P**) and negative for interleukin-6 (IL-6) and fibronectin (FN) (**Figure 4Q-T**).

Cerebrospinal fluid examination showed no central nervous system infiltration. Bone marrow examination showed atypical cells (**Figure 5A**, **5B**), although only a very small amount of specimen could be collected by fine needle aspiration due to a dry tap. Bone marrow biopsy revealed infiltration by the PTCL-NOS (**Figure 5C-H**). In addition, silver impregnation staining revealed MF (**Figure 5I**, **5J**). There was almost no normal hematopoietic tissue. Bone marrow blood was negative for JAK-2 V617F (data not shown). Based on the presence of bone marrow infiltration, the clinical stage was classified as IV B. Bone marrow immunostaining for cytokines showed that tumor cells were positive for PDGF, b-FGF, VEGF, TNF-α, IFN-γ, IL-1β, IL-2, and TGF-β (**Figure 6A-P**), and negative for IL-6 and FN (**Figure 6Q-T**).

As the lymphadenopathy became worse and the white blood cell count decreased further to 100/μL (likely caused by the bone marrow infiltration by the PTCL-NOS and MF), the patient was started on the first course of CHOP therapy (cyclophosphamide 750 mg/m^2: day 1, doxorubicin 50 mg/m^2: day 1, vincristine 1.4 mg/m^2 (max. 2 mg): day 1, prednisolone 100 mg/body: day 1-5) in early September. The lymphadenopathy improved (**Figure 2E-H**) and the white blood cell count also improved to 1,500/μL by

Table 1. Laboratory findings

CBC	WBC	500/mL ↓
	Band	16.0% ↑
	Seg	53.0%
	Ly	27.0%
	Mono	1.0% ↓
	Eo	2.0%
	Ba	1.0%
	RBC	311 × 10^4/mL ↓
	Hb	10.3 g/dL ↓
	Ht	32.0% ↓
	MCV	102.9 fl ↑
	MCH	33.1 pg
	Plt	6.8 × 10^4/mL ↓
	Reti	1.1%
Coagulation	PT	80%
	APTT	32.8 sec
	Fbg	203 mg/dL
	FDP	8.8 μg/mL
	DD	3.64 μg/mL
	AT3	53%
Biochemistry	T.P	5.1 g/dL ↓
	Alb	3.0 g/dL ↓
	AST	24 IU/L
	ALT	31 IU/L
	LDH	398 IU/L
	ALP	169 IU/L
	g-GTP	22 IU/L
	T-Bil	0.6 mg/dL
	BUN	16 mg/dL
	Cr	0.90 mg/dL
	CRP	1.9 mg/dL
	Ferritin	372.0 ng/mL
Immuno-serological findings	IgG	851 mg/dL ↓
	IgA	156 mg/dL
	IgM	25 mg/dL ↓
	Antinuclear antibodies	×40
	sIL-2R	5,410 U/mL
	HTLV-1 antibodies	-
	HIV antibodies	-
Serum cCytokine	PDGF-AB	845 pg/mL ↓ (10,499-29,463)
	VEGF	33 pg/mL ↑ (62-707)
	TGF-β1	2.40 ng/mL (1.56-3.24)
	High-sensitivity TNF-α	12.3 pg/mL ↑ (0.550-2.816)
	b-FGF	≤10 pg/mL (≤10)
	IL-6	5.7 pg/mL ↑ (≤4.0)
	IL-10	125 pg/mL ↑ (ND-5)
Urinalysis	No abnormalities	

Lymph node	G-Band	46,Y,add(X)(q22),del(6)(q?),-9,inv(9)(p12q13),del(11)(q?),-12,add(13)(q22),add(16)(q12.1),add(18)(q21),+mar1,+mar2
	TCRCβ1	Gene rearrangement detected
	IG(H)JH	Gene rearrangement detected
	CCR4 (immunostaining)	+
Bone marrow	G-Band	Poor growth
	TCRCβ1	Not tested due to insufficient specimen size
	IG(H)JH	Not tested due to insufficient specimen size
	JAK2V617F	No gene mutations (paraffin block specimen)

↑Denotes above the upper limit of the reference range, and ↓Denotes below the lower limit of the reference range. WBC, white blood cell; Seg, segment; Ly, lymphocyte; Mono, monocyte; Eo, eosinocyte; Ba, basophile; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular cell volume; MCH, mean corpuscular cell hemoglobin; Plt, plate; Reti, reticulocyte; PT, prothrombin time; APTT, activated partial thromboplastin time; Fbg, fibrinogen; FDP, fibrin fibrinogen degradation; DD, D-dimer; AT3, antithrombin III; T.P, total protein; Alb, albumin, AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-guanosine triphosphate; T-Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; HTLV-1, human T-cell leukemia virus-1; HIV, human immunodeficiency virus; PDGF-AB, platelet-derived endothelial growth factor-AB; FGF-basic, fibroblast growth factors-basic; IL-10, interleukin-10; G-Band, G-Banding; add, additional material of unknown origin; del, deletion; mar, marker chromosome; IG(H)JH, immunoglobulin heavy chain.

late September. Bone marrow examination showed a marked decrease of infiltration by the PTCL-NOS (**Figure 7A-H**) and improvement in the MF (**Figure 7I**, **7J**). Immunostaining for cytokines revealed positive staining for b-FGF, IFN-γ, IL-1β, IL-2, and IL-6 (**Figure 8C**, **8D**, **8I-N**, **8Q**, **8R**), but negative staining for PDGF, VEGF, TNF-α, FN, and TGF-β (**Figure 8A**, **8B**, **8E-H**, **8O**, **8P**, **8S**, **8T**). The patient was started on the second course of CHOP therapy in early October. In late October, the white blood cell count again decreased to 100/μL, and the serum LDH and sIL-2R levels increased. CT showed disappearance of the lymphadenopathy (**Figure 2I-L**), but bone marrow examination revealed progression of the PTCL-NOS infiltration (**Figure 9A-H**) and MF (**Figure 9I**, **9J**). Immunostaining for cytokines showed that the tumor cells were positive for PDGF, b-FGF, TNF-α, IFN-γ, IL-1β, TGF-β, and IL-6 (**Figure 10A**, **10B**, **10D-F**, **10H**, **10I**), but negative for VEGF, IL-2, and FN (**Figure 10C**, **10G**, **10J**). The patient was judged as being refractory to CHOP therapy, and the treatment was switched to mogamulizumab (1 mg/kg) in mid-November. He received two courses of mogamulizumab, however, the serum LDH and sIL-2R levels increased further, and the superficial lymphadenopathy also became worse. The treatment was changed again to CEPP therapy (cyclophosphamide 600 mg/m^2: day 1, 8, etoposide 70 mg/m^2: day 1-3, procarbazine 60 mg/m^2: day 1-10, prednisolone 60 mg/m^2: day 1-10) in early December. As of mid-December, the superficial lymphadenopathy had improved and the serum LDH and sIL-2R levels had decreased, however, the blood cell counts had not yet improved. We considered allogeneic transplantation, but the patient and his family declined to provide consent for the procedure.

Discussion

Primary myelofibrosis (MF) is characterized by clonal proliferation of megakaryocytes, monocytes and histiocytes, and the various cytokines produced by these cells, such as TGF-β, b-FGF, VEGF and TNF-α, are thought to be among the major causes of MF [1-3]. Malignant lymphoma complicated by MF is rare and the cause of MF in this condition remains unknown in many cases [4-12]. However, some studies have speculated that various cytokines may be responsible for the MF associated with malignant lymphoma, just as in the case of primary MF [2, 13-16].

To the best of our knowledge, there have been only a total of 15 reported cases of T-cell lymphoma complicated by MF, including the 7 cases of angioimmunoblastic T-cell lymphoma (AITL) previously reported by us and the present case (**Table 2**). The characteristics of these patients are summarized in **Table 3**. The medi-

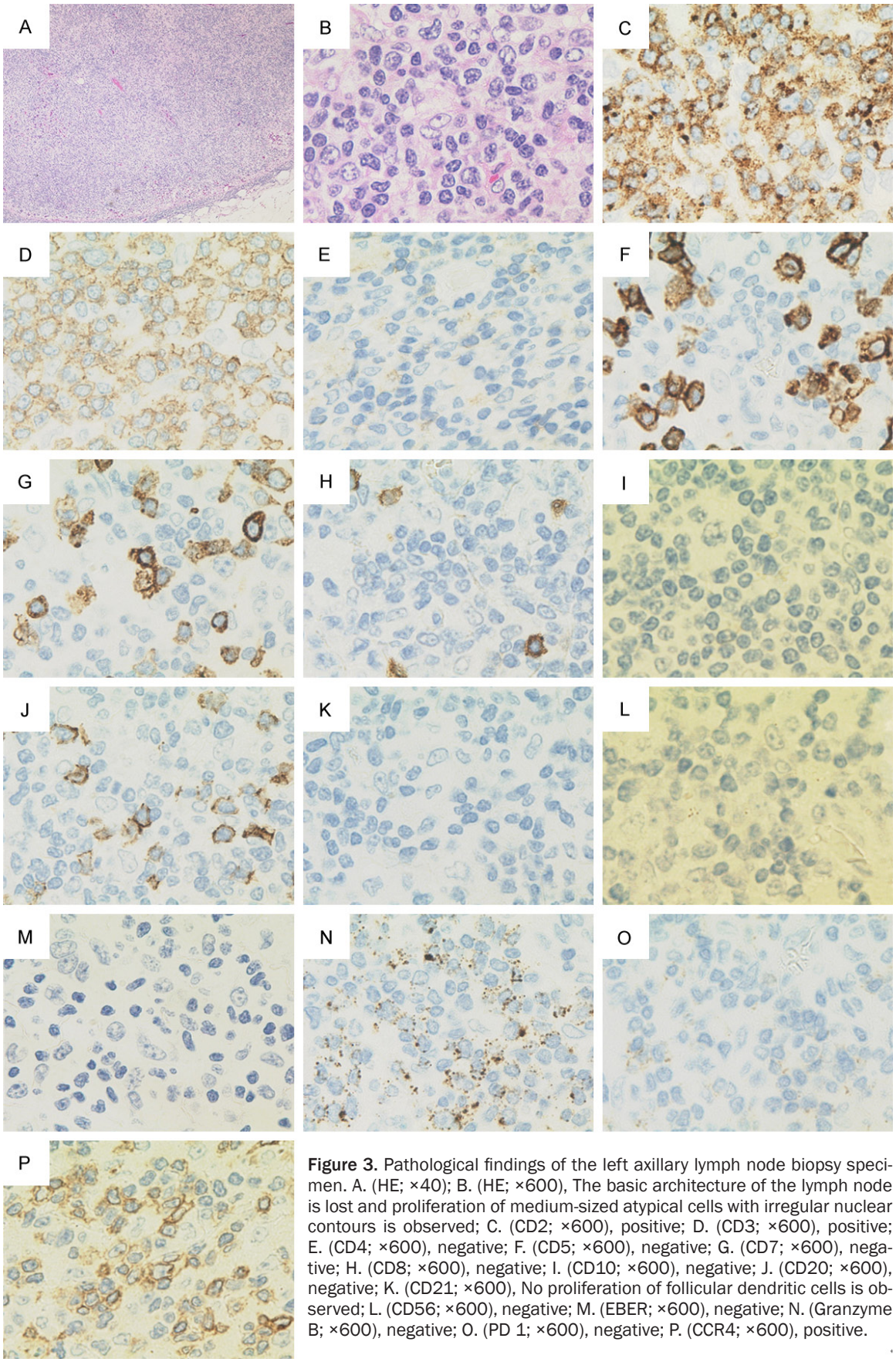

Figure 3. Pathological findings of the left axillary lymph node biopsy specimen. A. (HE; ×40); B. (HE; ×600), The basic architecture of the lymph node is lost and proliferation of medium-sized atypical cells with irregular nuclear contours is observed; C. (CD2; ×600), positive; D. (CD3; ×600), positive; E. (CD4; ×600), negative; F. (CD5; ×600), negative; G. (CD7; ×600), negative; H. (CD8; ×600), negative; I. (CD10; ×600), negative; J. (CD20; ×600), negative; K. (CD21; ×600), No proliferation of follicular dendritic cells is observed; L. (CD56; ×600), negative; M. (EBER; ×600), negative; N. (Granzyme B; ×600), negative; O. (PD 1; ×600), negative; P. (CCR4; ×600), positive.

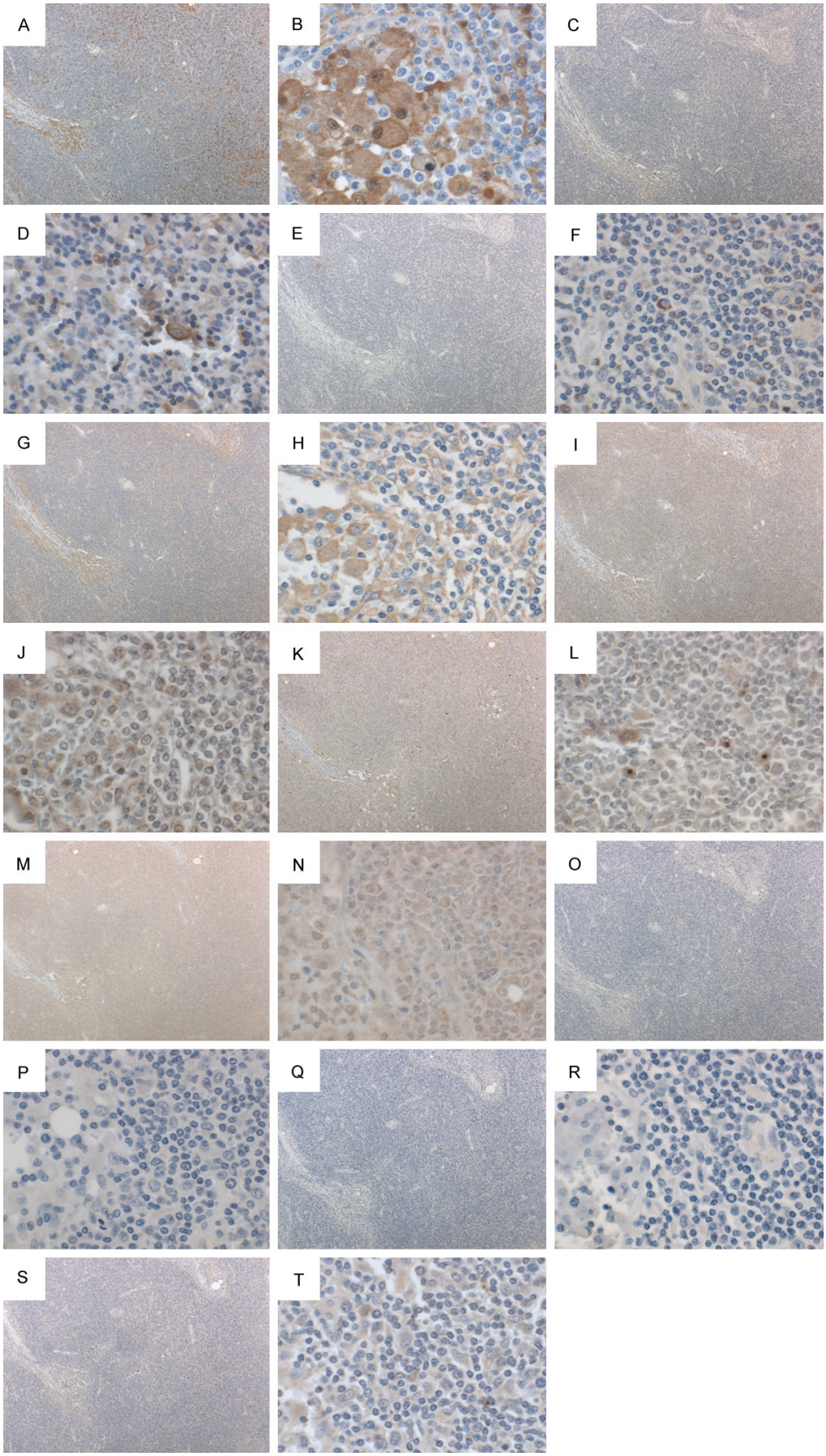
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Figure 4. Immunostaining of the left axillary lymph node biopsy specimen for cytokines. A. (PDGF; ×40), positive; B. (PDGF; ×400), positive; C. (b-FGF; ×40), positive; D. (b-FGF; ×400), positive; E. (VEGF; ×40), positive; F. (VEGF; ×400), positive; G. (TNF-α; ×40), positive; H. (TNF-α; ×400), positive; I. (IFN-γ; ×40), positive; J. (IFN-γ; ×40), positive; K. (IL-1β; ×40), positive; L. (IL-1β; ×400), positive; M. (IL-2; ×40), positive; N. (IL-2; ×400), positive; O. (TGF-β; ×40), positive; P. (TGF-β; ×400), positive; Q. (IL-6; ×40), negative; R. (IL-6; ×400), negative; S. (FN; ×40), negative; T. (FN; ×400), negative.

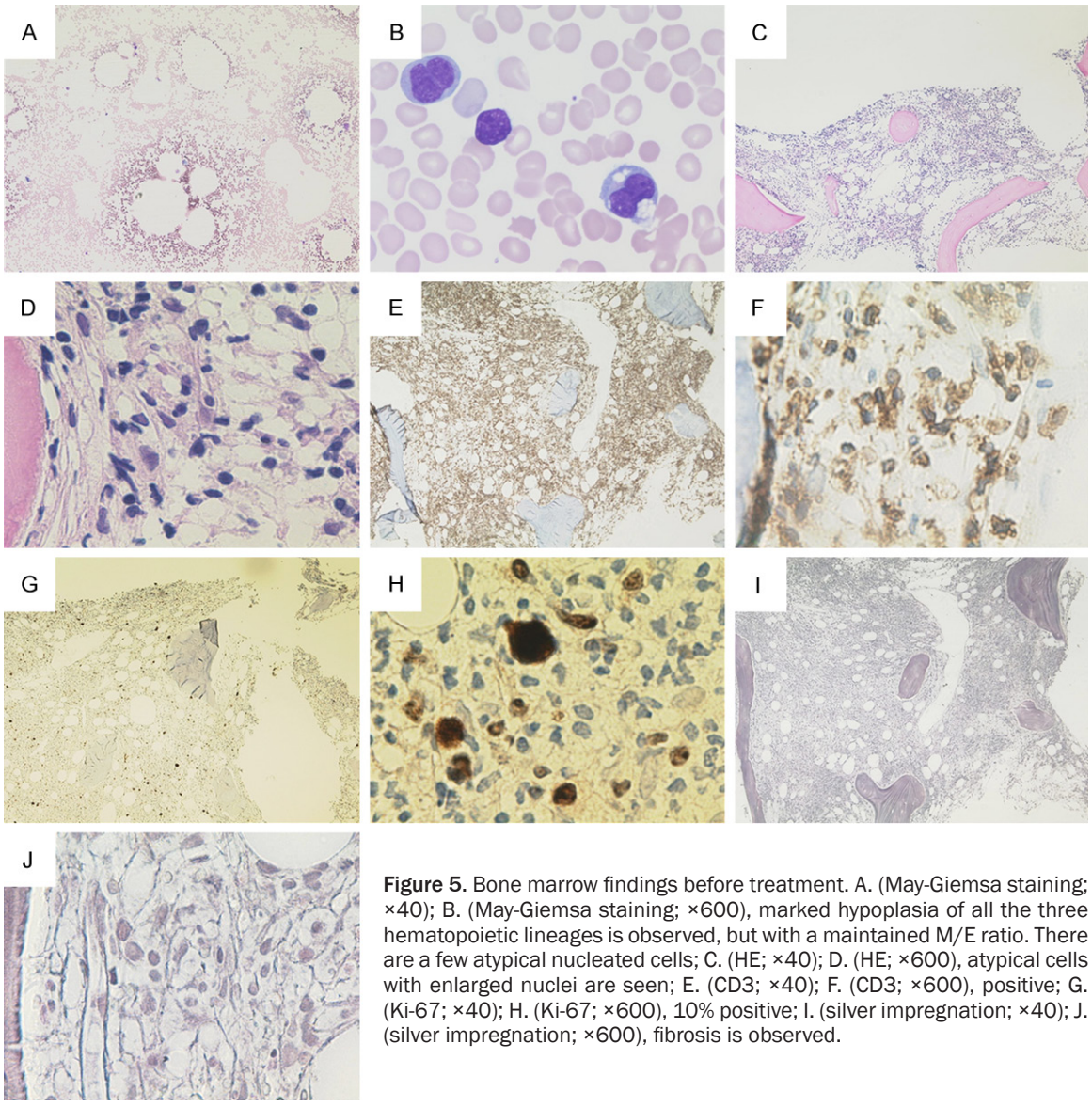

Figure 5. Bone marrow findings before treatment. A. (May-Giemsa staining; ×40); B. (May-Giemsa staining; ×600), marked hypoplasia of all the three hematopoietic lineages is observed, but with a maintained M/E ratio. There are a few atypical nucleated cells; C. (HE; ×40); D. (HE; ×600), atypical cells with enlarged nuclei are seen; E. (CD3; ×40); F. (CD3; ×600), positive; G. (Ki-67; ×40); H. (Ki-67; ×600), 10% positive; I. (silver impregnation; ×40); J. (silver impregnation; ×600), fibrosis is observed.

an age of the reported patients is 65 (19-90) years, and there were 8 men and 6 women (n = 14). AITL was the most common histological type of lymphoma (n = 7), followed in frequency by PTCL (n = 6). One patient had cytotoxic T-cell lymphoma and one had T-cell lymphoma, the details of which are unknown. All patients, but one, had an advanced stage of the disease (stage III, 2 patients, and stage IV, 12 patients).

Bone marrow infiltration was commonly seen: 12 of the 15 patients had bone marrow infiltration. Serum TGF-β is the cytokine that is most commonly thought to cause MF (n = 3) [13-15], followed in frequency by tumor cell b-FGF (detected by tumor cell immunostaining) (n = 2) [2, 16], tumor cell PDGF (detected by tumor cell immunostaining) (n = 2) [2; and the present case], and serum PDGF (n = 2) [14, 15],

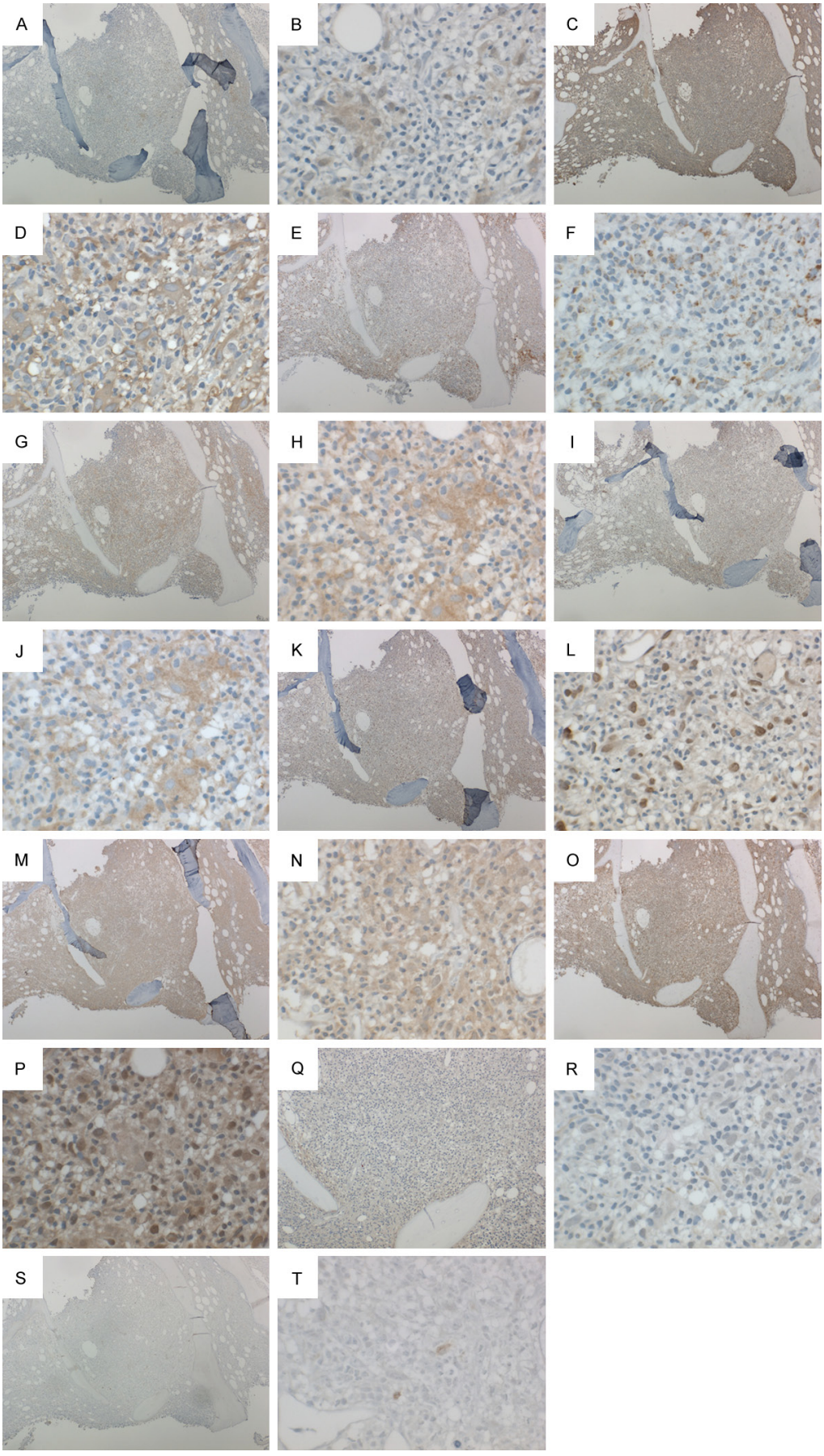
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Figure 6. Bone marrow immunostaining for cytokines before treatment. A. (PDGF; ×40), positive; B. (PDGF; ×400), positive; C. (b-FGF; ×40), positive; D. (b-FGF; ×400), positive; E. (VEGF; ×40), positive; F. (VEGF; ×400), positive; G. (TNF-α; ×40), positive; H. (TNF-α; ×400), positive; I. (IFN-γ; ×40), positive; J. (IFN-γ; ×40), positive; K. (IL-1β; ×40), positive; L. (IL-1β; ×400), positive; M. (IL-2; ×40), positive; N. (IL-2; ×400), positive; O. (TGF-β; ×40), positive; P. (TGF-β; ×400), positive; Q. (IL-6; ×40), negative; R. (IL-6; ×400), negative; S. (FN; ×40), negative; T. (FN; ×400), negative.

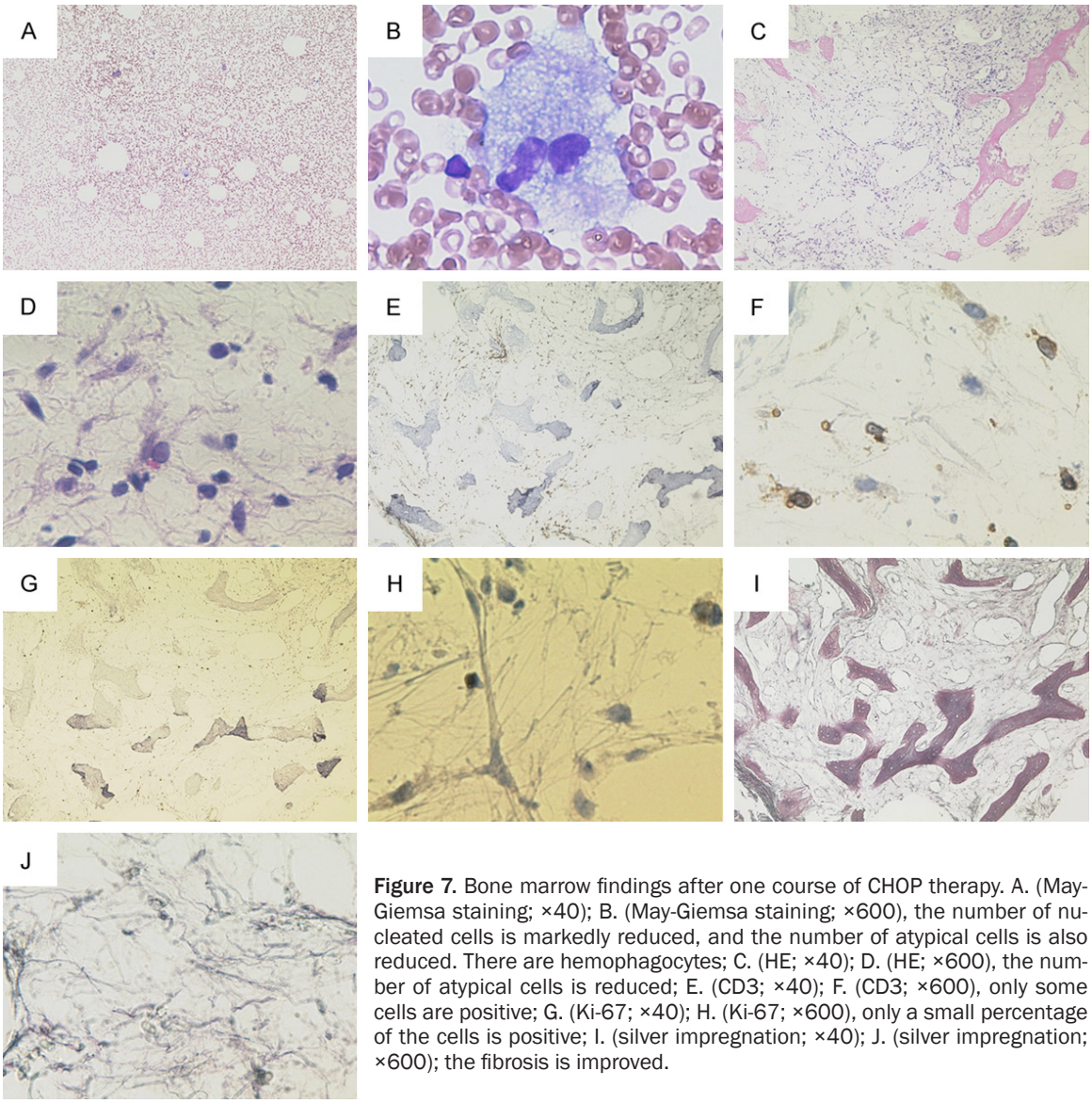

Figure 7. Bone marrow findings after one course of CHOP therapy. A. (May-Giemsa staining; ×40); B. (May-Giemsa staining; ×600), the number of nucleated cells is markedly reduced, and the number of atypical cells is also reduced. There are hemophagocytes; C. (HE; ×40); D. (HE; ×600), the number of atypical cells is reduced; E. (CD3; ×40); F. (CD3; ×600), only some cells are positive; G. (Ki-67; ×40); H. (Ki-67; ×600), only a small percentage of the cells is positive; I. (silver impregnation; ×40); J. (silver impregnation; ×600); the fibrosis is improved.

although in some patients, multiple cytokines were thought to cause MF (n = 6: tumor cell cytokines [detected by immunostaining alone], n = 2; serum cytokines alone, n = 3; both tumor cell and serum cytokines, n = 1 [the present case]). Tumor cell TGF-β (detected by tumor cell immunostaining), tumor cell TNF-α (detected by tumor cell immunostaining), and serum TNF-α were thought to cause MF only in the present case. The cytokines causing the MF remained unknown in as many as 7 patients. Various treatments for the T-cell lymphoma were employed, and 8 patients improved. One patient improved only to deteriorate subsequently, one did not improve, and one deteriorated, suggesting that the treatments for T-cell lymphoma do not always improve the MF and careful observation is required. In addition, 8

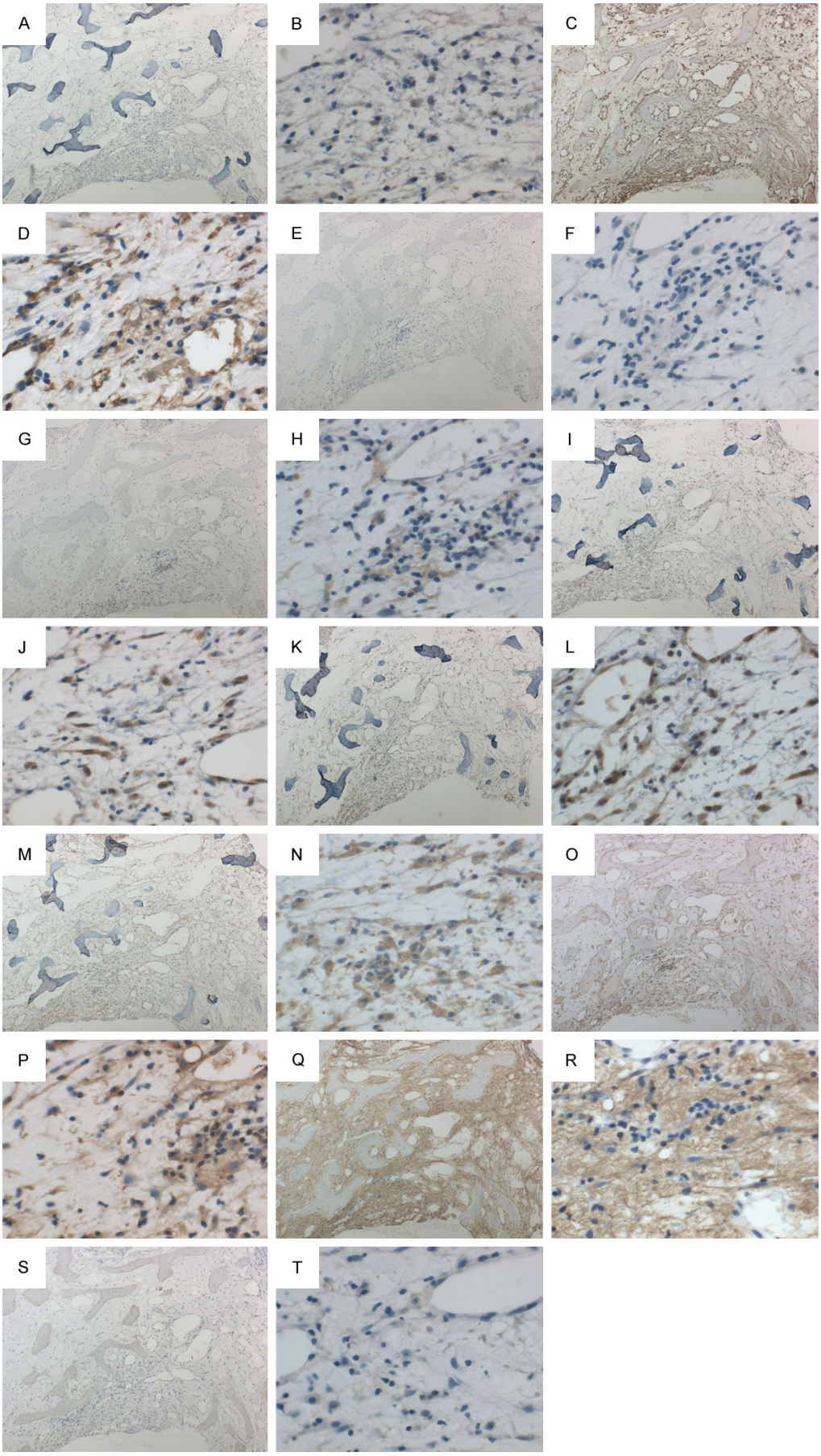
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Figure 8. Bone marrow immunostaining for cytokines after one course of CHOP therapy. A. (PDGF; ×40), negative; B. (PDGF; ×400), negative; C. (b-FGF; ×40), positive; D. b-FGF; ×400), positive; E. (VEGF; ×40), negative; F. (VEGF; ×400); negative; G. (TNF-α; ×40), negative; H. (TNF-α; ×400), negative; I. (IFN-γ; ×40), positive; J. (IFN-γ; ×40), positive; K. (IL-1β; ×40), positive; L. (IL-1β; ×400), positive; M. (IL-2; ×40), positive; N. (IL-2; ×400), positive; O. (TGF-β; ×40), negative; P. (TGF-β; ×400), negative; Q. (IL-6; ×40), positive; R. (IL-6; ×400), positive; S. (FN; ×40), negative; T. (FN; ×400), negative.

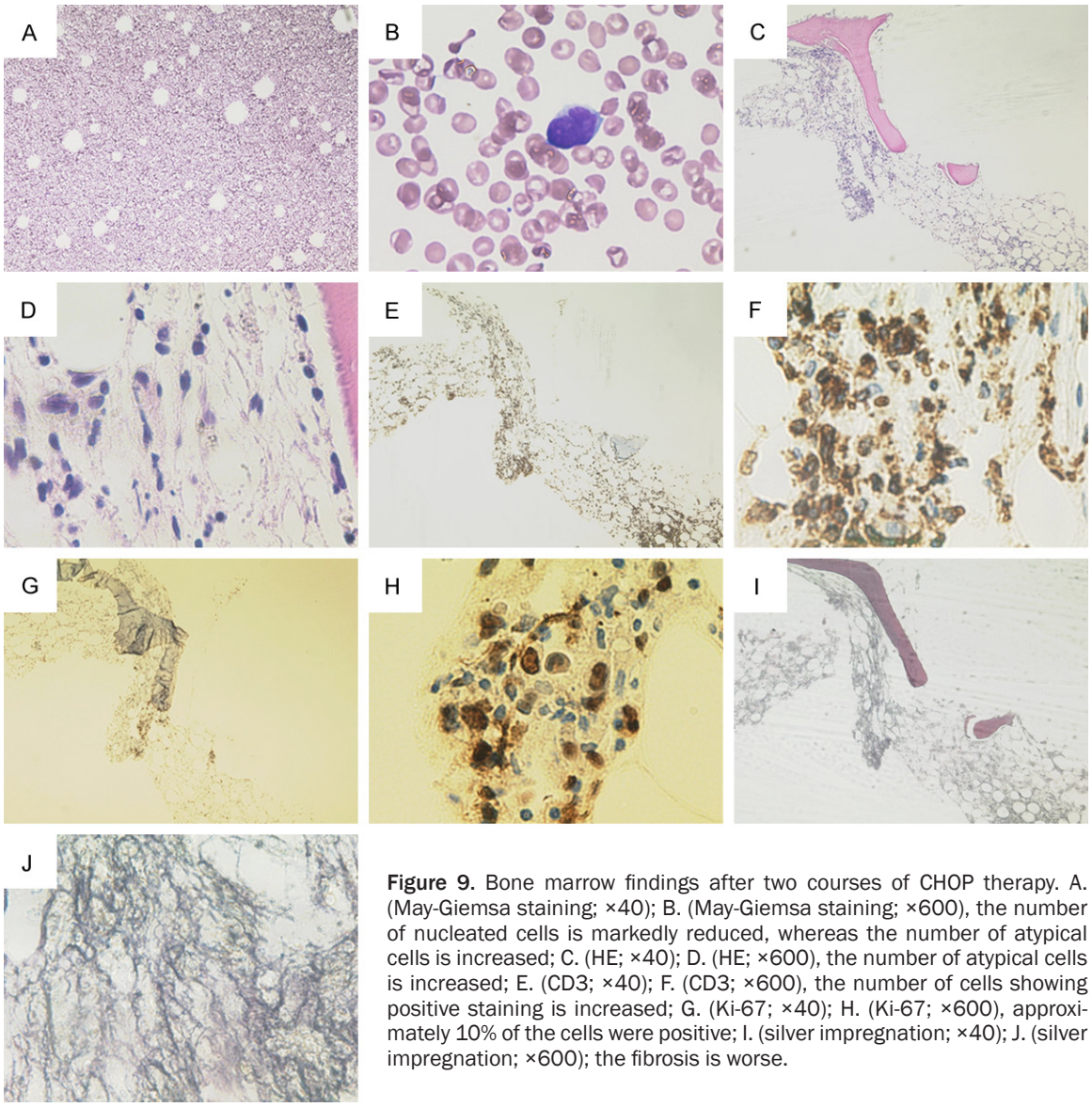

Figure 9. Bone marrow findings after two courses of CHOP therapy. A. (May-Giemsa staining; ×40); B. (May-Giemsa staining; ×600), the number of nucleated cells is markedly reduced, whereas the number of atypical cells is increased; C. (HE; ×40); D. (HE; ×600), the number of atypical cells is increased; E. (CD3; ×40); F. (CD3; ×600), the number of cells showing positive staining is increased; G. (Ki-67; ×40); H. (Ki-67; ×600), approximately 10% of the cells were positive; I. (silver impregnation; ×40); J. (silver impregnation; ×600); the fibrosis is worse.

patients died, suggesting that the disease carries a very poor prognosis [4, 5, 8-11, 13, 16].

The cytokines that were thought to be responsible for the MF in the present case are discussed. PDGF, b-FGF, VEGF, TNF-α, IFN-γ, IL-1β, IL-2, and TGF-β were immunohistochemically detected in both the lymph nodes and the bone marrow with MF before treatment (**Figures 4**, **6**; **Table 4**). After one course of CHOP therapy, the MF in the bone marrow improved, and the tumor cells in the bone marrow became negative for PDGF, VEGF, TNF-α, and TGF-β (**Figure 8**; **Table 4**). However, the cells became positive again for PDGF, TNF-α, and TGF-β (**Figure 10O**, **10P**), along with progression of the MF, after two courses of CHOP therapy (**Figure 9**), suggesting the contribution of these cytokines to

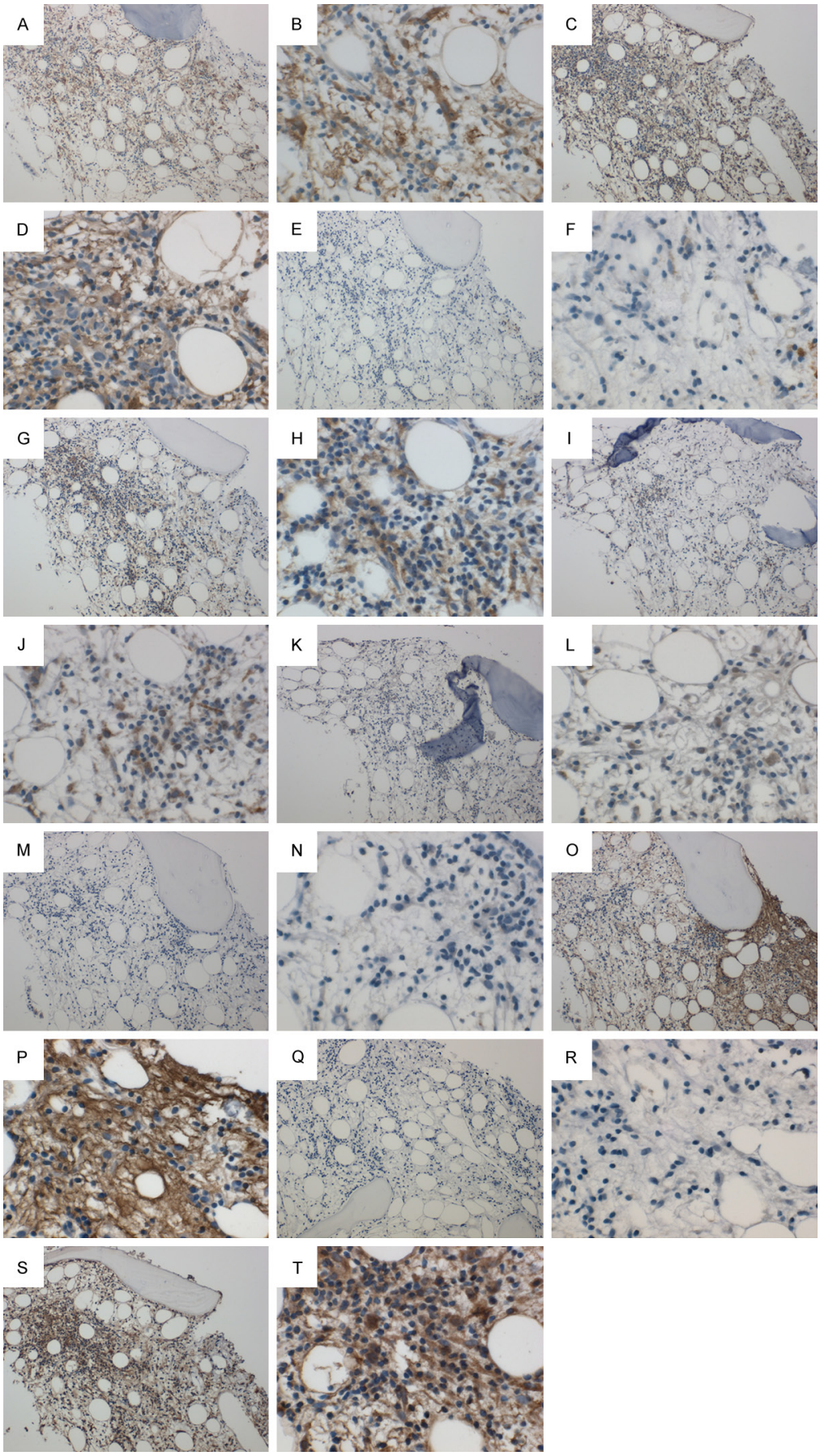
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Figure 10. Bone marrow immunostaining for cytokines after two courses of CHOP therapy. A. (PDGF; ×40), positive; B. (PDGF; ×400), positive; C. (b-FGF; ×40), positive; D. (b-FGF; ×400), positive; E. (VEGF; ×40), negative; F. (VEGF; ×400), negative; G. (TNF-α; ×40), positive; H. (TNF-α; ×400), positive; I. (IFN-γ; ×40), positive; J. (IFN-γ; ×40), positive; K. (IL-1β; ×40), positive; L. (IL-1β; ×400), positive; M. (IL-2; ×40), negative; N. (IL-2; ×400), negative; O. (TGF-β; ×40), positive; P. (TGF-β; ×400), positive; Q. (IL-6; ×40), positive; R. (IL-6; ×400), positive; S. (FN; ×40), negative; T. (FN; ×400), negative.

Table 2. List of reports of T-cell lymphoma complicated by myelofibrosis

Case	Age/sex	Histological type	Stage	BM Infiltration	Cytokine	Treatment	Results (T-cell lymphoma)	Results (BMF)	Outcome	Ref.
1	67/F	PTCL-NOS	IV	+	NA	PSL CHOP I.T.	Improved→ relapse CNS infiltration	NA	Died of sepsis	[4]
2	90/M	PTCL-U	IV	+	b-FGF (immuno-staining)	-	Deterioration	NA	Died of liver dysfunction after 1 M	[5]
3	68/M	PTCL-U	IV	+	TGF-β (serum)	THP-COP 2 courses	Deterioration	Deteriora-tion	Died of DIC after 9 M	[6]
4	69/M	PTCL	IV	+	NA	Chemotherapy 3 courses	NA	Improved	Died of bone marrow suppression due to BMF after 2Y6 M	[7]
5	46/F	T-cell lymphoma (details unknown)	IV	+	NA	Splenectomy CHOP Salvage therapy (ifosfamide, carboplatinum, etoposide)	Improved→ relapse Improved→ relapse Improved→ Hematopoietic stem cell transplantation being considered	Improved	11 M, surviving	[8]
6	19/F	Cytotoxic T- cell lymphoma	IV	+	PDGF TGF-β (serum)	CY, DXR, VCR, PSL	PR→ Allogeneic transplantation	Improved	1 Y, remission, surviving	[9]
7	65/F	PTCL	IV	+	NA	DVP CHOP I.T. (MTX, Ara-C) Cranial irradiation, 40 Gy	Improved	Improved	10 M, surviving	[10]
8	68/M	PTCL-NOS	IV	+	PDGF TNF-α TGF-β (immuno-staining)	CHOP Mogamulizumab CEPP	Improved→ Relapse Deterioration Improved	Improved→ Deterio-ration, No improve-ment, unknown	7 M, surviving	This case
9	63/M	AITL	IV	+	0NA	PSL 50 mg	Improved	NA	Died of systemic candidemia after 6 M	[11]
10	NA/NA	AITL	II or great-er	-	NA	PSL	CR→ relapse	NA	Died of sepsis after 25 M	[12]
11	69/F	AITL	III	-	NA	PSL 60 mg	Improved	Improved	Died of biliary cirrhosis after 15 M	[13]
12	47/M	AITL	IV	+	NA	PSL 30 mg PSL 60 mg	Improved→ relapse→ improved	Not improved	Died of pulmonary aspergillosis after 3 m	[14]

13	55/F	AITL	IV	+	NA	PSL, VCR	PR	Improved	12 M, surviving	[15]
14	56/M	AITL	III	-	PDGF TGFβ (serum)	CHOP ESHAP CHASE	CR→ relapse→ CR	Improved	12 M, surviving	[16]
15	65/M	AITL	IV	+	PDGF b-FGF (immu-no-staining)	CHOP ESHAP Auto mPSL pulse WBI	CR→ CNS relapse	Improved	13 M, surviving	[2]

BM, bone marrow; BMF, bone marrow fibrosis; M, male; F, female; PSL, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; I.T., intrathecal administration of anticancer agents; NA, not available; PTCL-U, Peripheral T-Cell lymphoma-unspecified; y, years; m, months; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone; DIC, disseminated intravascular coagulation; CY, cyclophosphamide; DXR, doxorubicin; VCR, vincristine; DVP, daunomycin, vincristine, prednisolone; MTX, methotrexate; Ara-C, cytarabine; Gy, gray; TNF-α, tumor necrosis factor-α; CEPP; cyclophosphamide hydrate, etoposide, prednisolone, procarbazine hydrochloride; CR, complete remission; PR, partial remission; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; CHASE, cyclophosphamide, cytarabine, etoposide, dexamethasone; MCVAC, ranimustine, cytarabine, etoposide, cyclophosphamide; Auto, autologous peripheral blood stem cell transplantation; mPSL, methylprednisolone; WBI, whole brain irradiation.

Table 3. Summary of reports of T-cell lymphoma complicated by myelofibrosis

Age/sex	Median age: 65 (19-90) years
	Male: female = 8:6 (n = 14)
Histological type	AITL: n = 7
	PTCL: n = 6
	Cytotoxic T-cell lymphoma: n = 1
	NA: n = 1
Stage	Stage II or greater: n = 1
	Stage III: n = 2
	Stage IV: n = 12
BM infiltration	+: n = 12
	-: n = 3
Cytokine (Multiple cytokines in the same patients)	b-FGF (immunostaining): n = 2
	TGF-β (immunostaining): n = 1
	TGF-β (serum): n = 3
	PDGF (immunostaining): n = 2
	PDGF (serum): n = 2
	TNF-α (immunostaining): n = 1
	TNF-α (serum): n = 1
	NA: n = 9
	(n = 6)
Treatment	PSL: n = 7
	mPSL: n = 1
	CHOP: n = 6
	THP-COP: n = 1
	DVP: n = 1
	CEPP: n = 1
	Mogamulizumab: n = 1
	CEPP: n = 1
	ESHAP: n = 2
	CHASE: n = 1
	Auto: n = 1
	I.T.: n = 2
	None: n = 1
	Chemotherapy: n = 3
	Salvage therapy: n = 1
	Splenectomy: n = 1
	WBI: n = 2
Results (T-cell lymphoma)	Improved: n = 9
	Improved→ Deterioration: n = 3
	Deterioration: n = 2
	NA: n = 1
Results (BMF)	Improved: n = 8
	Improved→ Deterioration: n = 1
	No improvement: n = 1
	Deterioration: n = 1
	NA: n = 4
Outcome	Surviving: n = 7
	Died: n = 8

PSL, prednisolone; NA, not available; mPSL, methylprednisolone; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone; DVP, daunomycin, vincristine, prednisolone; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; CHASE,

cyclophosphamide, cytarabine, etoposide, dexamerthasone; Auto, autologous peripheral blood stem cell transplantation; I.T., intrathecal administration of anticancer agents.

Table 4. List of changes of the results of immunostaining of the lymph nodes and bone marrow for cytokines

	LN	BM	BM	BM
	Before CHOP	Before CHOP	After one course of CHOP	After two courses of CHOP
BMF		+	-	+
PDGF	+	+	-	+
b-FGF	+	+	+	+
VEGF	+	+	-	-
TNF-α	+	+	-	+
IFN-γ	+	+	+	+
IL-1β	+	+	+	+
IL-2	+	+	+	-
TGF-β	+	+	-	+
IL-6	-	-	+	+
FN	-	-	-	-

Table 5. List of changes of the serum levels of cytokines

	Before CHOP	After one course of CHOP	After two courses of CHOP
BMF	+	±	+
PDGF (pg/ml) (10,499-29,463)	845	≤780	1010
b-FGF (pg/ml) (≤10)	≤10	≤10	≤10
VEGF (pg/ml) (62-707)	33	23	32
TNF-α (pg/ml) (0.550-2.816)	12.3	2.4	5.7
IFN-γ	n.a.	n.a.	n.a.
IL-1β	n.a.	n.a.	n.a.
IL-2	n.a.	n.a.	n.a.
TGF-β (ng/ml) (1.56-3.24)	2.40	1.25	1.24
IL-6 (pg/ml) (≤4.0)	5.7	3.9	11.6
FN	n.a.	n.a.	n.a.

BMF, bone marrow fibrosis; n.a., XXXX.

MF. The tumor cells remained negative for VEGF as the MF progressed, suggesting the lack of contribution of VEGF to the MF (**Figure 10E**, **10F**).

In regard to the serum cytokines (**Table 5**), only the serum TNF-α level was elevated (12.3 pg/mL) prior to the start of the treatment, while the serum levels of PDGF, VEGF, and TGF-β did not increase. After one course of CHOP therapy, the serum TNF-α level decreased to 2.4 pg/mL (within the normal range), associated with improvement of the MF. However, the serum TNF-α level increased again to 5.7 pg/mL with progression of the MF. TNF-α was the only cytokine whose level was increased in the serum and was also detected in the tumor cells by immunostaining. It was unclear whether only TNF-α, whose level in the serum was increased and which was also detected by immunostaining, was involved in the development of the MF, or whether PDGF and TGF-β, which were detected in the tumor cells by immunostaining but did not increase in the serum, were also involved. This is the first reported case of MF associated with lymphoma in which TNF-α is speculated as the cause of the MF.

This is the only report published so far investigating cytokines by both serum assay and tumor cell immunostaining (**Table 2**). It is considered important to identify the causes of MF by accumulating the results of measurements of cytokines by both serum assay and tumor cell immunostaining in patients with T-cell lymphoma and MF and determining the specificity and sensitivity of the assays.

It was reported that administration of neutralizing anti-GM-CSF or anti-IL-3 antibodies improved MF in mice with primary MF [3], suggesting that the use of neutralizing anti-cytokine antibodies should be considered for MF that is unresponsive to treatment for T-cell lymphoma, like in the present case.

In this case, as TNF-α was speculated as one of the causes of the MF, administration of anti-TNF-α antibody (infliximab, which is covered by the national health insurance only if used for rheumatoid arthritis or refractory uveoretinitis associated with Behcet's disease in Japan)

may be considered in the future. In addition, since there was almost no normal hematopoietic tissue in the bone marrow, and we considered allogeneic transplantation; however, the patient declined to provide consent for this procedure.

Disclosure of conflict of interest

None.

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