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Case Report

Recurrent Crow-Fukase Syndrome Associated with Increased Serum Levels of Vascular Endothelial Growth Factor: A Case Report and Review of the Literature

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Mineta, M., Hatori, M., Sano, H., Hosaka, M., Kokubun, S., Hiroki, E., Hatakeyama, A. and Ogasawara, T. *Recurrent Crow-Fukase Syndrome Associated with Increased Serum Levels of Vascular Endothelial Growth Factor: A Case Report and Review of the Literature*. Tohoku J. Exp. Med. 2006, **210** (3), 269-277 —— Crow-Fukase syndrome (CFS) is a rare multi-system disorder, characterized by polyneuropathy, organomegaly, endocrinopathy, M-proteins, skin changes and anasarca, with or without myeloma. The pathophysiology, diagnosis, and treatment of CFS are controversial. CFS may be associated with the overproduction of vascular endothelial growth factor (VEGF). However, there have been no reports of monitoring the serum VEGF level after recurrence, to the best of our knowledge. We report a 54-year-old man with CFS presenting with a 3-year history of ascites, anasarca, weakness of the lower extremities, and plasmacytoma in the scapula. At the initial examination, the VEGF level was 1,590 pg/ml (the VEGF level of a healthy control, 78.4 ± 75.2 pg/ml). After initial treatment with chemotherapy and irradiation of the affected shoulder, the VEGF level decreased to 154 pg/ml and the symptoms disappeared. Twenty one months later, gate disturbance and anasarca recurred, and the VEGF level was over 2,000 pg/dl. After total scaplectomy, the VEGF level decreased to 730 pg/dl and the symptoms disappeared. The serum level of VEGF well correlated to the clinical course of the patient. In conclusion, measurement of the VEGF level is useful for diagnosing CFS and for monitoring its clinical course. ———— Crow-Fukase syndrome; vascular endothelial growth factor (VEGF); polyneuropathy

Crow-Fukase syndrome (CFS) was initially reported by Crow (1956) and Shimpo et al. (1968). CFS is a rare multi-system disorder characterized by polyneuropathy(P), organomegaly(O), endocrinopathy(E), M-proteins(M), skin changes(S) (POEMS syndrome) and anasarca (Bardwick et al. 1980). Fifty five to 99% of CFS patients have bone lesions (plasmacytoma) and 41 to 52% patients have a solitary lesion (Bardwick et al. 1980; Takatsuki and Sanada 1983; Nakanishi

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et al. 1984; Soubrier et al. 1994).

Vascular endothelial growth factor (VEGF) is a potent, multifunctional cytokine that induces angiogenesis and microvascular hyperpermeability (Senger et al. 1983; Ferrara and Henzel 1989; Hashiguchi et al. 2000). Brown et al. (1992, 1993) reported that VEGF expression was increased in tumor cells and that VEGF is an important cytokine in wound healing. Watanabe et al. (1996, 1998) reported that the serum VEGF levels increased in patients with CFS and that they decreased after treatment. Nakano et al. (2001) and Endo et al. (2002) suggested that VEGF was produced by plasma cells. The overproduction of VEGF causes the characteristic clinical manifestations of CFS (Hashiguchi et al. 2000).

There have been no reports of monitoring the VEGF level after recurrence, to the best of our knowledge. We report a case of recurrent CSF, in which the serum VEGF level was monitored serially.

Case Report

A 54-year-old man presented with an approximately three year-history of ascites, anasarca, weakness of the lower extremities, skin pigmentation on the whole body, and swelling of the left scapula. At the age of 17, the patient underwent surgery for chronic sinusitis and was blood transfusion. At the age of 51, he suffered from cirrhosis due to hepatitis C. At the age of 54, polyneuropathy due to hepatitis C virus infection was suspected. The patient came to our hos-

Table 1. Laboratory data.

WBC (/μl)	500	BUN (mg/dl)	16
RBC (/μl)	$3{,}070 \times 10^3$	Cr (mg/dl)	0.53
Hb (g/dl)	11.9	CRP (mg/dl)	0.21
PLT (/μl)	1.15×10^3	TSH (μIU/ml)	5.52
TB (mg/dl)	1.6	FT3 (pg/ml)	1.08
GOT (IU/l)	14	FT4 (ng/dl)	0.71
GPT (IU/l)	8	FBS (mg/dl)	122
γ-GTP (IU/l)	10	TC (mg/dl)	79
ChE (IU/l)	34	TG (mg/dl)	36
TTT (KU)	7.9	VEGF (pg/ml)	1,590
ZTT (IU/l)	27.7		
NH_3 (μg/dl)	184	HCV-Ab	Positive
TP (g/dl)	5.5	M-protein	Increase
alb (g/dl)	2.0	(Ig-G γ type)	
γ-glb (%)	43.8	BJP	Negative
Ig-G (mg/dl)	2,656		
Ig-A (mg/dl)	285		
Ig-M (mg/dl)	59		

WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet; TB, total bilirubin; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase isozyme; ChE, cholinesterase; TTT, thymol turbidity test; ZTT, zinc sulfate turbidity test; HCV-Ab, hepatitis C virus antibody; TP, total protein; alb, albumin; γ-glb, gamma globlin; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; VEGF, vascular endtherial growth factor; BJP, Bence-Jones proteinuria.

pital because of gait disturbance.

At the initial examination, laboratory findings were as follows: serum C-reactive protein (CRP) 0.21 mg/dl, thyroid stimulating hormone 5.52 μIU/ml (normal range 0.5 to 5.0), total protein 5.5 g/dl, and albumin 2.0 g/dl (Table 1). Immunoelectrophoresis showed that M-protein was the Ig-G lambda type. Cryoglubolin was negative. Electromyography showed axonal polyneuropathy. Nerve biopsy was not performed because of the cirrhosis. Bone scintigram showed a single hot spot in the left scapula (Fig. 1). Plain radiogram revealed a mixed osteosclerotic and osteolytic scapula tumor (Fig. 2). CT showed osteolysis in the glenoid, coracoid process, and neck of the scapula (Fig. 3). Biopsy of the left scapula revealed that the cells had dense eosino-

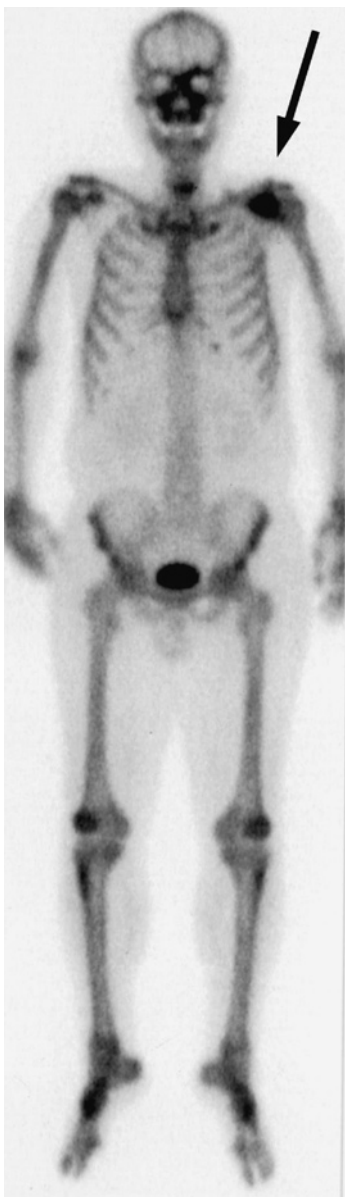

Fig. 1. Bone scintigram.
There was a single hot spot on the left scapula.

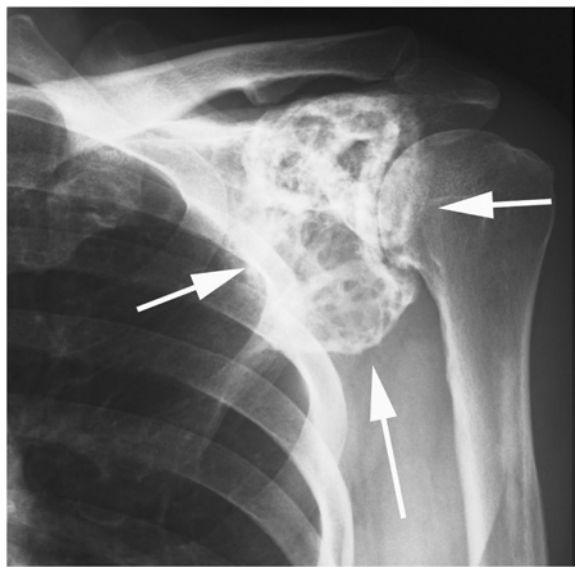

Fig. 2. Plain radiogram of the left shoulder.
Plain radiogram revealed a mixed osteosclerotic and osteolytic scapula tumor.

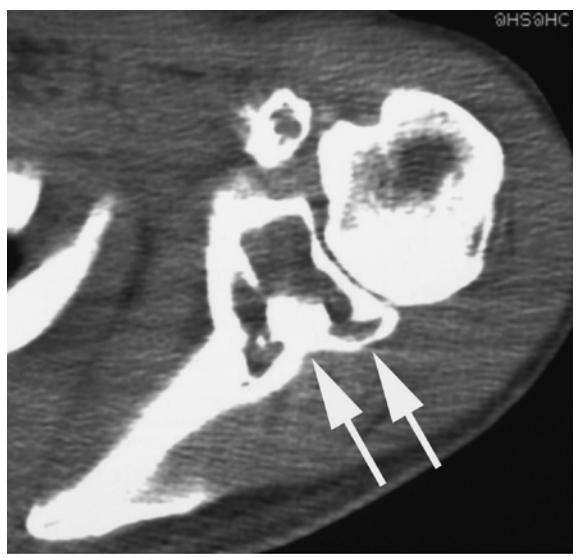

Fig. 3. CT of the left shoulder.
CT showed osteolysis in the glenoid, the coracoid process and the neck of the scapula.

philic cytoplasm and speckled patterned nuclear-chromatin (Fig. 4). The bone tumor of the scapla was diagnosed as plasmacytoma. Bone marrow examination was normal. Bence-Jones proteinuria was not detected. No evidence of overt myeloma was found. Brain MR image showed no abnormalities.

The diagnosis of CFS was made based on the findings of polyneuropathy, organomegary (splenomegaly), edema including ascites and pleural effusions, endocrinopathy (hypothyroidism), M-proteinemia, skin changes, bone lesion, and increased VEGF level (1,590 pg/ml).

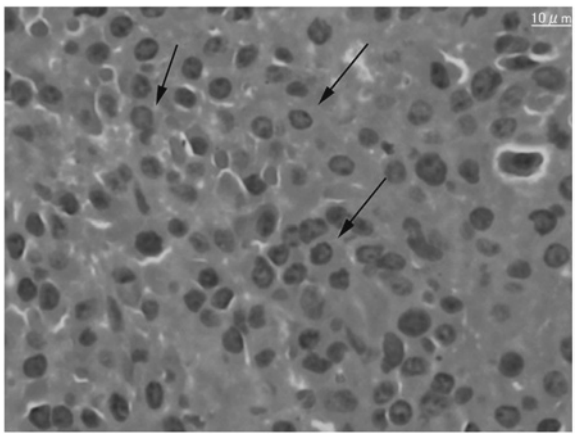

Fig. 4. Histology (hematoxylin-eosin stain).
Biopsy of the left scapula revealed that the cells had dense eosinophilic cytoplasm and speckled patterned nuclear-chromatin. The scapula bone tumor was diagnosed as plasmacytoma. Arrows indicate representative tumor cells.

Initially, the patient was treated with prednisolone (PSL), cyclophosphamide (CPA), plasma exchange therapy (PX), and radiotherapy (RT) (three Gy per 20 fractions) (Fig. 5). During the treatment of CFS, the patient had high temperature of up to 39° and nausea. Brain CT showed an abscess. PSL administration was reduced and antibiotics started. At one month after starting treatment, the VEGF level decreased to154 pg/dl, and the patient could walk using a short leg brace. After five months the anasarca, ascites and pleural effusions disappeared, and the patient was discharged. The patient was stable during the next 21 months.

At 19 months after being discharged, the serum VEGF level increased to 1,040 pg/ml. Two months later, the patient again suffered from anasarca and difficulty in walking due to weakness of the lower extremities, and the VEGF level increased to over 2,000 pg/dl (Fig. 6). Laboratory findings were as follows: white blood cell count (WBC), 4,200 /μl; red blood cell count, 3.95 × 10^6/μl; hemoglobin, 13.3 g/dl; platelet, 144 × 10^3/μl; and CRP, 0.1 mg/dl. Bone scintigram showed a single hot spot in the left scapula. The range of

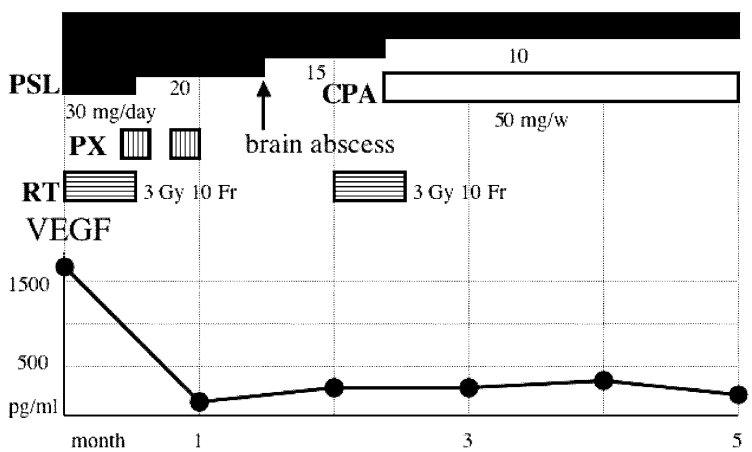

Fig. 5. Treatment and serum VEGF.
One month after starting treatment, the serum VEGF levels decreased. The patient could walk with a short leg brace.
PSL, prednisolone; CPA, cyclophosphamide; PX, plasma exchange therapy; RT, radiotherapy.

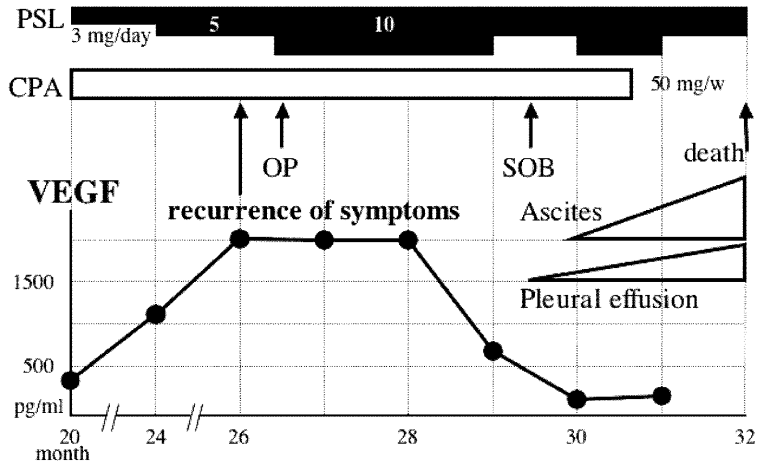

Fig. 6. Progress after surgery.
Two months after surgery, the serum VEGF levels decreased to 730 pg/dl.
PSL, Prednisolone; CPA, cyclophosphamide; SOB, shortness of breath.

movement of the left shoulder was limited to 90 degrees of elevation. We diagnosed this condition as a recurrence of CFS, and performed left total scaplectomy (Fig. 7).

The range of movement of the left shoulder was limited to 20 degrees of elevation. At one month after surgery, the anasarca and weakness of the lower extremities disappeared, and the patient could walk again. At two months after surgery, the VEGF level had decreased to 730 pg/dl and the patient discharged from our hospital.

At three months after surgery, the patient felt shortness of breath and was re-admitted. The patient's temperature remained within a normal range. The VEGF CRP, and WBC levels were 219 pg/ml, 0.17 mg/dl, and 4,300/μl, respectively. The patient had pleural effusions and ascites that were difficult to be managed. The daily urine output was 3 l/day and the ascites amounted to 12 l/week. Dehydration occurred on the next day with the limitation of drinking. There was hypoproteinemia (total protein, 5.5g/dl; albmin, 2.0 g/dl), dysfunction of kidneys and liver (blood urea nitrogen, 74 mg/dl; creatinine, 1.15mg/dl total bilirubin, 4.7 mg/dl; glutamate oxaloacetate transaminase, 23 IU/l; and glutamate pyruvate transaminase, 32 IU/l). The patient died of dehydration. The cause of the dehydration was suspected to have been multiple organ failure caused by

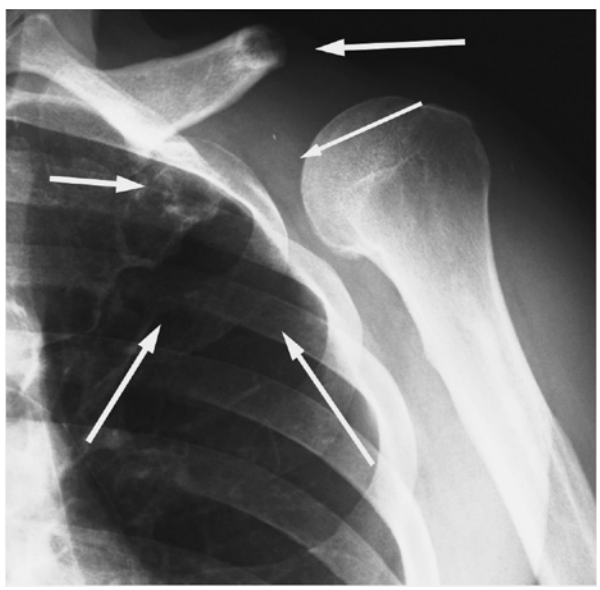

Fig. 7. Postscaplectomy.
Left total scaplectomy was performed. The range of movement of the left shoulder was limited to 20 degree of elevation.

hepatic failure, which occurred 32 months after the original diagnosis of CFS. The exact cause of the pleural effusions, ascites and polyurea was unknown because autopsy was not permitted by the patient's family.

The patient and his family were informed that data from the case would be submitted for

publication, and gave their consent.

Discussion

CFS

CFS is a rare multisystemic disorder, initially reported by Crow (1956) and Shimpo (1968). The syndrome shows polyneuropathy, organomegaly, endocrinopathy, M-proteins, skin changes and anasarca, with or without myeloma (Bardwick et al. 1980; Nakanishi et al. 1984). Fifty five to 99% of CFS patients have bone lesions (plasmacytoma) and 41 to 52% have a solitary lesion (Bardwick et al. 1980; Takatsuki and Sanada 1983; Nakanishi et al. 1984; Soubrier et al. 1994). The median age at presentation was 51 years and 63% of patients are men. The median survival was 165 months. The most commonly identified causes of death are cardiorespiratory failure and infection (Dispenzieri et al. 2003). The symptoms of CFS vary depending on the patient. The cause of CFS remains unknown.

VEGF

VEGF is a potent, multifunctional cytokine that induces angiogenesis and microvascular hyperpermeability (Senger et al. 1983; Ferrara and Henzel 1989; Hashiguchi et al. 2000). Senger et al. (1983) found that tumor ascites fluids from guinea pigs, hamsters, and mice contain activity that rapidly increases the microvascular permeability. Ferrrara and Henzel (1989) found a growth factor for vascular endothelial cells in media conditioned by bovine pituitary follicular cells and proposed to name this factor VEGF. Nakano et al. (2001) and Endo et al. (2002) suggested that VEGF was produced by plasma cells. Hashiguchi et al. (2000) showed that platelets were a major source of VEGF and that VEGF was released during platelet aggregation by physiological stimulation.

Watanabe et al. (1998) suggested that the overproduction of VEGF is closely related to the pathogenesis of CFS. The mean VEGF level in patients with CFS (1,673.2 ± 1,165.7 pg/ml [S.D.]) is significantly higher than in healthy controls (78.4 ± 75.2 pg/ml [S.D.]). In CFS patient, the local VEGF concentration is markedly elevated by the aggregation of platelets containing excessive VEGF and their adhesion to vascular walls, resulting in the excessive physiological activities of VEGF.

Correlation between CFS and VEGF

The overproduction of VEGF causes the characteristic clinical manifestations of CFS (Hashiguchi et al. 2000). VEGF is thought to induce polyneuropathy, organomegary, skin changes and edema in CFS. Polyneuropathy is suggested to be induced by endothelial edema due to an alteration of the blood-nerve barrier caused by the VEGF-induced hyperpermeability, and the endothelial cell abnormalities due to the intravascular coagulation activated by VEGF (Arimura et al. 1997). The high serum and peripheral nerve VEGF were both associated with more severe endoneurial vessel involvement and nerve damage (Scarlato et al. 2005). Such an increase of VEGF is not found in demyelinating polyneuropathy (Watanabe et al. 1998). Organomegaly is characterized by marked vascular proliferation and may be associated with VEGF. Skin changes, especially hemangioma, may be induced by angiogenesis due to VEGF, and edema may be induced by the VEGF-induced hyperpermeability (Ozaki et al. 2004). Since CFS patients have often been reported to show increased VEGF levels (Watanabe et al. 1996, 1998; Henzan et al. 1999; Nakano et al. 2001; Arimura et al. 2003; Tokashiki et al. 2003; Ozaki et al. 2004; Takai et al. 2004; Yoritaka et al. 2004). VEGF would appear to be a useful diagnostic marker for CFS (Arimura et al. 1997; Henzan et al. 1999).

Diagnosis of CFS

Two major criteria and at least a minor criterion are thought to be required for the diagnosis of CFS (Dispenzieri et al. 2003). In the present case, the presence of two major criteria (polyneuropathy and M-proteinemia) and more than 3 minor criteria (sclerotic bone lesion, organomegary [splenomegaly], edema including ascites and pleural effusions, endocrinopathy [hypothyroidism], and skin changes) satisfied the Dispenzieri's criteria. Splenomegaly, edema

including ascites and pleural effusions and skin changes are sometimes observed in patients with cirrhosis. The median time between the onset of symptoms and diagnosis is 15 months (range, 3 to 120 months) (Dispenzieri et al. 2003). In the present case, the time between onset and diagnosis was about three years because of the difficulty in distinguishing between liver cirrhosis and CFS. Recently, a retrospective analysis of 629 patients using the Dispenzieri's criteria suggested that these may not be definitive (Ofran and Elinav 2005). Arimura et al. (2003) reported new criteria in which a major criterion and at least 2 minor criteria are needed for the diagnosis of CFS (Table 2). The minor criteria included the increased VEGF level. The present case also met Arimura's criteria, and the increased serum VEGF was useful for making a diagnosis of CSF.

Treatment of CFS

The treatment for CFS has not been standardized. It may include corticosteroids (Nauck et al. 1998), chemotherapy (Kuwabara et al. 1997; Badros el al. 2005), bone marrow transplant (Soubrier et al. 2002), peripheral blood stem cell transplantation (Jaccard et al. 2002), and surgery (Ichikawa et al. 2001) and RT (Kelly et al. 1981). For an isolated plasmacytoma RT is indicated and for widespread lesions chemotherapy is indicated (Dispenzieri et al. 2004). In the present case, first the patient received treatment with PSL, CPA, PX and RT (Fig. 5). Subsequently, the patient underwent left total scaplectomy because of CFS recurrence (Figs. 6 and 7). Both the first and second therapies lead to clinical improvement and a decrease in the VEGF level. Watanabe et al. (1998) reported the usefulness of monitoring VEGF in CFS. They measured the VEGF level in ten CFS cases and noticed a decrease of VEGF in seven cases after treatment. Of these seven cases, five showed great improvement in the symptoms and the other two cases had complete relief.

Case reports of measurement of VEGF for CFS

In the previous 17 out of 27 case reports, the VEGF level decreased and the symptoms improved after treatment (Watanabe et al. 1996, 1998; Arimura et al. 1997; Soubrier et al. 1998; Henzan et al. 1999; Niimi et al. 2000; Ichikawa et al. 2001; Shinde et al. 2001; Araki et al. 2002; Endo et al. 2002; Jaccard et al. 2002; Koga et al. 2002; Minamitani et al. 2002; Lewerenz et al. 2003; Takahashi et al. 2003; Takakura et al. 2003; Tokashiki et al. 2003; Baba et al. 2004; Matsui et al. 2004; Ozaki et al. 2004; Takai et al. 2004; Yoritaka et al. 2004; Badros et al. 2005; Imai et

TABLE 2. Criteria for the diagnosis of POEMS syndrome.

Major criteria	I	Polyneuropathy (chronic and sensorimotor disturbance)
Minor criteria	I	M protein
	II	Organomegary (lymphadenopathy, hepatomegaly, splenomegaly, kidney enlargement)
	III	Anasarca (ascites, pleural effusions)
	IV	Skin change (hyperpigmentation, hypertichosis, angiomatosis)
	V	Endocrinopathy (impotence, menoxenia, glucose intolerance, thyroidal dysfunction)
	VI	Papilledema
	VII	Increase serum VEGF (> 500 pg/ml)

A major criterion and 3 minor criteria are needed for the diagnosis of CFS (Arimura et al. 2003).

al. 2005; Scarlato et al. 2005; Kuwabara et al. 2006; Sanada et al. 2006). In the present case as well, after treatment the VEGF level decreased and was correlated with the clinical symptoms (Figs. 5 and 6). To the best of our knowledge, it is noteworthy that there have been no reports of monitoring the VEGF level after recurrence. In the present case, we traced the VEGF level during the entire clinical course of the patient from the initial diagnosis until his death and confirmed that the VEGF level well correlated with the clinical condition including the recurrence.

In conclusion

VEGF is not only an important diagnostic marker for CFS but also useful for evaluating the clinical course.

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