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# An autopsy case of TAFRO syndrome with multiple cerebral infarctions caused by small vessel pathology

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*Dear Sirs,*

TAFRO syndrome is a systemic inflammatory disorder manifesting as: thrombocytopenia, anasarca, fever, reticulin myelofibrosis and/or renal insufficiency, and organomegaly [1,2]. Some patients take a fatal clinical course due to vascular hyperpermeability, plasma volume reduction, and multiorgan failure. There are only a few reports of TAFRO syndrome complicated with cerebral infarctions, which were associated with large-vessel occlusion [3–5]. Here, we report an autopsy case of a TAFRO syndrome patient who presented with multiple cerebral infarctions due to small-vessel pathology.

A 60-year-old male was admitted to our hospital with left hemiplegia. He had a history of cramp-fasciculation syndrome, deep vein thrombosis, hypertension, and chronic kidney disease. He had taken several medications including prednisolone and warfarin. On admission, his blood pressure was 153/99 mmHg, body temperature was 35.9 degrees Celsius, and he showed no edema. On neurological examination, he was alert and presented with mild left hemiplegia and disturbed superficial sensation of the left limbs. A blood test revealed elevated levels of creatinine (1.99 mg/dL), C-reactive protein (2.37 mg/dL), soluble interleukin-2 receptor (1170 U/mL), and PT-INR (3.10). The platelet count was normal (325,000 /μL). Brain MRI showed high-intensity areas in the right corona radiata and other deep white matter areas on diffusion-weighted imaging (Fig. 1A-C). Neither microbleeds nor stenosis of major vessels was shown. There were no embolic sources detected by 12-lead and Holter electrocardiography, transthoracic and transesophageal echocardiography, or ultrasound of the carotid artery and leg veins. Although we started intravenous antiplatelet therapy and continued oral warfarin, MRI revealed a new asymptomatic infarction in the left caudate head on day 5 (Fig. 1D). Additional examinations revealed markedly elevated serum VEGF (723 pg/mL) and mildly elevated serum IL-6 (10.7 pg/mL). Cerebrospinal fluid showed elevated protein (126 mg/dL), a normal cell count, and no evidence of malignancy. Whole-body CT revealed splenomegaly and bilateral pleural effusions (Fig. 1E). PET-CT showed mild retention of $^{18}$F-fluorodeoxyglucose in left inguinal, bilateral external iliac, and paraaortic lymph nodes. Lymph node biopsy showed Castleman disease-like histology, including atrophy of the germinal center, enlargement of the interfollicular space, and increase of plasma cells (Fig. 1F-G). Bone marrow biopsy revealed an increase of megakaryocytes and no evidence of malignant lymphoma and myelofibrosis. Random skin biopsy performed twice revealed no evidence of intravascular lymphomatosis. Brain MRI showed an increase of novel infarctions in the deep white matter and basal ganglia without occlusion of major arteries on days 13 and 16 (Fig. 1H-I). Subsequently, he gradually developed fever, edema, renal failure, and thrombocytopenia (69,000/μL). Based on the criteria, we diagnosed him with TAFRO syndrome. Although we administered methylprednisolone pulse therapy twice, he developed multiorgan failure and died on day 28. Autopsy revealed small infarctions in the cerebrum, cerebellum, pontine, and spinal cord. Fibrous thickening and atherosclerotic change were observed in the intima of cerebral arteries. Occlusion, recanalization, and unstable plaques were noted in arterioles (Fig. 1J-K). There was no evidence of vasculitis or a clot.

We reported a patient with multiple cerebral infarctions refractory to antithrombotic therapies with systemic inflammation, thrombocytopenia, and characteristic pathological findings of lymph nodes. He was diagnosed with TAFRO syndrome based on the disease criteria [6]. The increased pleural effusions and mild splenomegaly helped to make a diagnosis, and elevations of IL-6 and VEGF were also consistent with the syndrome [2].

The complication of cerebral infarctions with TAFRO syndrome is relatively rare, and only three patients were previously reported (Table 1) [3–5]. They developed infarctions mainly in the cortical area of ACA and MCA territories. Disseminated intravascular coagulation (DIC) was observed in two patients, and the occlusion or stenosis of major vessels probably triggered by atherosclerotic change or vasculitis was also noted. These cases suggested that the cerebral infarctions in TAFRO syndrome could be caused by coagulation abnormalities, major vessel stenosis, and embolisms. On the other hand, the present patient did not show a DIC state during the majority of the clinical course, and neither clinical imaging nor autopsy showed major vessel occlusions, vasculitis, or embolisms. Although the pathogenesis of our patient remains largely unknown, his infarctions were dominantly located in subcortical and deep white matter areas where blood perfusion is relatively oligemic, suggesting that intravascular dehydration or failed microperfusion may be associated with the pathogenesis. The autopsy suggested not only atherosclerosis but also endothelial injury of cerebral

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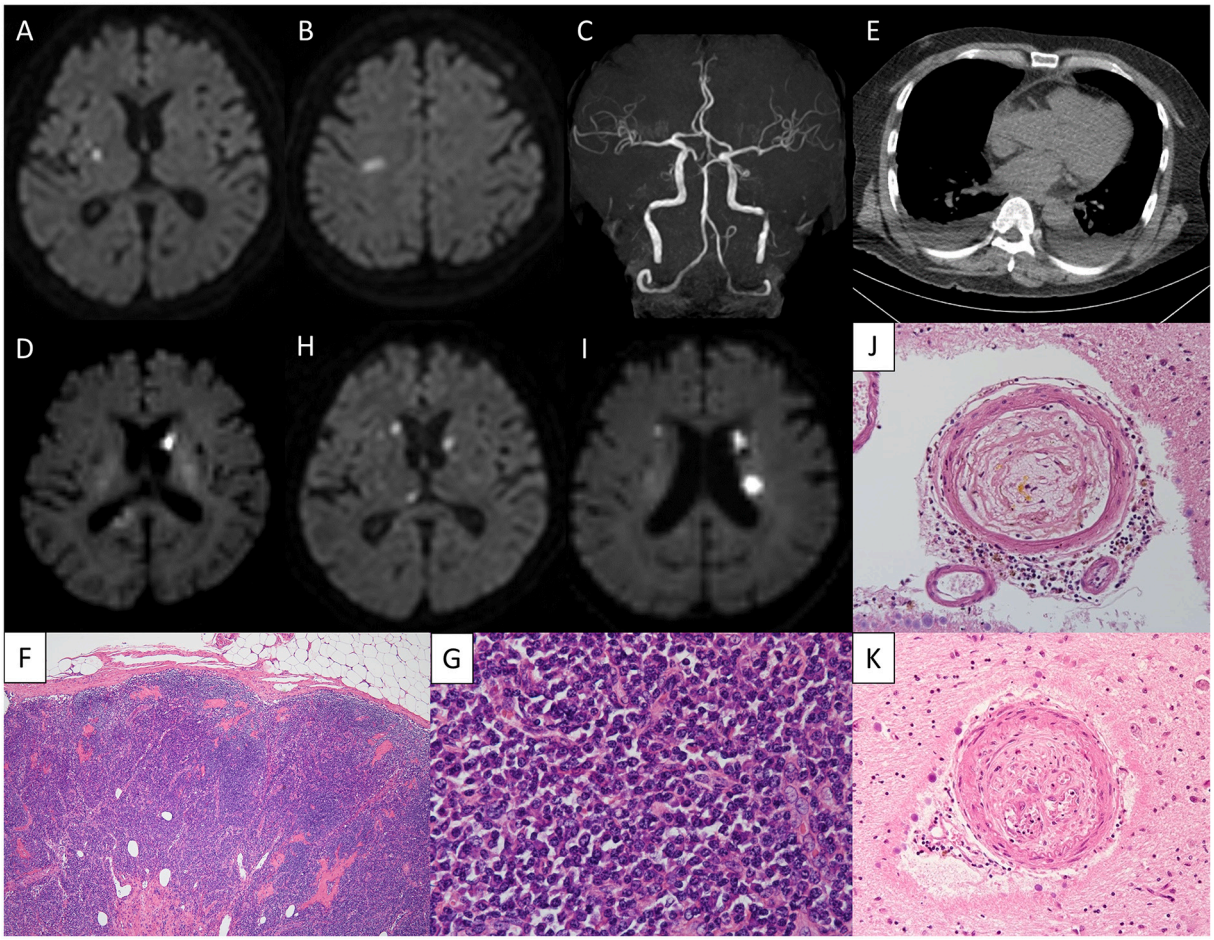


**Fig. 1.** Brain MRI, chest CT, and pathological findings of the patient.
A-C. Brain MRI revealed multiple acute infarctions on diffusion-weighted imaging (DWI) (A, B) and MRA showed no stenosis of major vessels (C) on admission.
D. DWI identified a new infarction in the left caudate head on day 5.
H, I. DWI showed multiple new infarctions mainly in medullary artery areas on day 13 (H) and 15 (I).
E. Chest CT revealed bilateral pleural effusion.
F-G. Biopsy of left the inguinal lymph node showed atrophy of the germinal center, enlargement of the interfollicular space (F), and an increase of plasma cells (G).
J-K. Autopsy revealed fibrous thickening of the intima and occlusion of the lumen (J) and recanalization of cerebral small vessels (K), which suggested endothelial injury and atherosclerosis. There was no evidence of vasculitis or clots.

**Table 1**
Cerebral infarctions in patients with TAFRO syndrome.

| Case | Age / sex | Past history | Cerebral infarctions | Major vessel lesions | Coagulation abnormalities | Suggested pathogenesis | Reference |
|---|---|---|---|---|---|---|---|
| Patient 1 | 17 y.o / male | Tetralogy of Fallot, Goldenhar syndrome | Infarctions at bilateral ACA areas | None | DIC | Hypercoagulability in DIC, Intravascular dehydration | [3] |
| Patient 2 | 72 y.o / male | Hypertension, Hyperlipidemia | A cerebral infarction with light hemiparesis | Atherosclerosis with a fibrin clot at right MCA in autopsy | DIC | Vascular occlusion by DIC, Atherosclerosis | [4] |
| Patient 3 | 42 y.o / female | Psoriasis | Infarctions at bilateral ACA and MCA areas | Bilateral ICA occlusions on MRA | None | Vasculitis of cerebral arteries | [5] |
| Present patient | 60 y.o / male | Cramp fasciculation syndrome, Deep vein thrombosis | Multiple infarctions in subcortical areas | None | None | Intravascular dehydration, Disrupted microperfusion | |

ACA: anterior cerebral artery, DIC: disseminated intravascular coagulation, MCA: middle cerebral artery, ICA: internal carotid artery, MRA: magnetic resonance angiography.

small vessels, which is consistent with the report that glomerular microangiopathy was a common finding in TAFRO syndrome [7]. We hypothesized that the endothelial injury and hyperpermeability due to increases of VEGF and IL-6 might cause insufficient local circulation and ischemia. Based on this hypothesis, more intense immunotherapies targeting the lymphocytes producing these cytokines such as

cyclosporine may have been effective [2].

In conclusion, our case suggests that TAFRO syndrome could cause cerebral infarctions by various pathogeneses including small-vessel lesions. Early diagnosis and intense immunotherapies are needed for successful treatment of the disease.

## Declaration of Competing Interest

None.

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