Infectious Mononucleosis Complicated with Acute Cerebral Infarction: A Case Report

Jiann-Jy Chen[1,2], Hsin-Feng Chang[3,4], Chih-Yang Liu[5], Dem-Lion Chen[6]

Abstract-

Purpose: Infectious mononucleosis (IM) complicated with a neurological manifestation, including acute cerebellar ataxia, Guillain-Barre syndrome, meningitis, encephalitis, cranial nerve palsies, optic neuritis or transverse myelitis, has been rarely reported; however, IM complicated with acute cerebral infarction has never been reported in the literature.

Case Report: A 49-year-old man with diabetic mellitus suffered from IM with fever, pharyngitis, parotiditis with lymphadenopathies, thrombocytopenia and splenomegaly. After two weeks of conservative treatment, left upper limb paresis and left hemihypesthesia occurred. Neuroimaging demonstrated acute ischemic stroke involving the right frontal lobe. In view of the underlying infection, immediate intravenous rt-PA was not recommended; hence, oral aspirin 100 mg daily was prescribed and he received regular rehabilitation in the subsequent follow up.

Conclusion: Although IM is known to be self-limited, it could contribute to acute cerebral infarction, which is a rare IM neurological complication.

Key Words: infectious mononucleosis, fever, parotiditis, cerebral infarction

Acta Neurol Taiwan 2015;24:25-29

INTRODUCTION

Infectious mononucleosis (IM), commonly known as glandular fever, has the classic triad of fever, pharyngitis and lymphadenopathy as well as the presence of heterophil antibodies and atypical lymphocytes. IM complicated with splenomegaly, hepatitis, and mild neutropenia has been commonly reported, and can make a sufferer quite ill though full recovery is usual in 2 to 3 weeks[(1)]; but a neurological complication, including acute cerebellar ataxia, Guillain-Barre syndrome, meningitis, encephalitis, cranial nerve palsies, optic neuritis or transverse myelitis,

From the [1]Department of Neuro-Medical Scientific Center, Buddhist Tzu Chi General Hospital, Taichung Branch, Taichung; [2]Department of Otorhinolaryngology, Taoyuan General Hospital, Ministry of Health and Welfare, Executive Yuan, Taoyuan; [3]Faculty of Chinese Medicine, Chinese Medical College, China Medical University, Taichung; [4]Department of Medical Education, China Medical University Hospital, Taichung; [5]Department of Neurology, Buddhist Tzu Chi General Hospital, Taipei Branch, New Taipei, Taiwan; [6]G-Home Clinic for Otorhinolaryngology and Neurology, Kaohsiung, Taiwan.
Received February 5, 2014. Revised April 28, 2014.
Accepted January 12, 2015.

Correspondence to: Chih-Yang Liu, MD. No. 289, Jianguo Road, Sindian District, New Taipei City 23142, Taiwan
E-mail: jiannjy@yahoo.com.tw

has been rare[2-5]. Of ischemic stroke patients, 25–35% had a recent infection[6], but IM complicated with stroke never been reported in the literature in the literature. Herein we presented such a rare case of IM complicated with acute cerebral infarction.

CASE REPORT

A 49-year-old male taxis driver had O blood type; weight, 65 kg; height, 159 cm; and body mass index, 25.7 kg/m^2. He had been addicted to 1.5 packs of cigarette per day for three decades. He did not suffer hypertension, heart disease or hyperlipidemia, but had regularly received hypodermal injection of insulin for type II diabetic mellitus for two years.

He presented with sore throat, right facial swelling and fever for two days. Vital signs were measured showing body temperature, 37.9°C; blood pressure, 127/90 mmHg; heart rate, 118/min; and respiration rate, 20/min. Physical examination showed that the bilateral tonsils and retropharyngeal mucosa were congested swelling; besides, a fixed tender congested swelling about 7 × 10 cm was palpated over his right neck level II, including the right parotid region, and the other neck levels were unremarkable. Blood examination reported leukocytosis with monocytosis, atypical lymphocytosis and thrombocytopenia. Moreover, both blood amylase and C-reactive protein (CRP) were high (Table 1A). Cytomegalovirus (CMV) IgM, mumps and human immunodeficiency virus (HIV) I/II antibody were negative. Although anti-Epstein-Barr virus (EBV) nuclear antigen (EBNA) titer was 1/40 (normal reference, 1/1 or 1/10), anti-EBV viral capsule antigen (VCA) IgM was negative, and anti-EBV VCA IgG was positive. The biochemistry, fasting blood sugars, and lipid profile were within normal ranges. Contrast enhanced computed tomography disclosed swelling of right parotid gland and neighboring lymph nodes (Fig. 1A). Abdomen ultrasonography showed moderate splenomegaly. Thus, he was diagnosed with IM with fever, pharyngitis, parotiditis with lymphadenopathies, thrombocytopenia and splenomegaly. Then he was admitted for supportive treatment. Oral prednisolone (Donison, China Chemical & Pharmaceutical Co, Taiwan) 10 mg twice daily was prescribed. The blood sugar was controlled with diabetic mellitus diet and hypodermal injection of insulin (NovoMix 30 Penfill 300 IU/3 ml, Novo Nordisk A/S, Denmark) 12 units twice daily, before breakfast and dinner.

Two weeks later, the sore throat remitted, right neck mass became a non-tender cold mass of less than 1 × 1 cm, and body temperature was 36.5°C, but his left upper limb became too weak to lift up in the morning. There was not any headache, vertigo, tinnitus, hearing block, dysarthria, dysphagia, dysphonia, blurred vision or diplopia. He was still clear. His judgement, orientation, memory, attention, and calculation were all intact. Neurologic examinations showed olfactory sensations to coffee powders were good, and the six directions of eyeball movements were smooth; but left central-type facial palsy was noted. There was not any lingual weakness, palatal weakness, gargle reflex absence, swallowing difficult, hemineglect or cortical sign. The neck was flexible without any meningeal sign. The muscle power was grade 0 (Medical Research Council Scale) in the left upper limb and grade 5 in the other three limbs. His left-side facial, limb and trunk surfaces were less sensitive to pain. The deep tendon reflex was 2+ in

Table 1.

Common blood examinations					
	A.	B.	C.	D.	Normal reference
WBC (k/μL)	18.29↑	24.14↑	19.28↑	3.93↓	4.0~10.80
Neutrophil (%)	48.0	42.5	37.0↓	20.0↓	40.0~74.0
Monocyte (%)	37.0↑	21.0↑	26.0↑	7.0	3.4~11.0
Lymphocyte (%)	8.0↓	17.0↓	18.0↓	70↑	19.0~49.0
Atypical lymphocyte (%)	4.0↑	1.5↑	2.0↑	0	0.0~1.0
Platelet (103/μL)	84↓	85↓	62↓	164	130~400
CRP (mg/dL)	16.2↑	16.3↑	4.74↑	0.4	0.0~0.8
Amylase (u/L)	560↑	62	44	38	36~128

"↑" and "↓" represent the value above and below the normal reference, respectively.

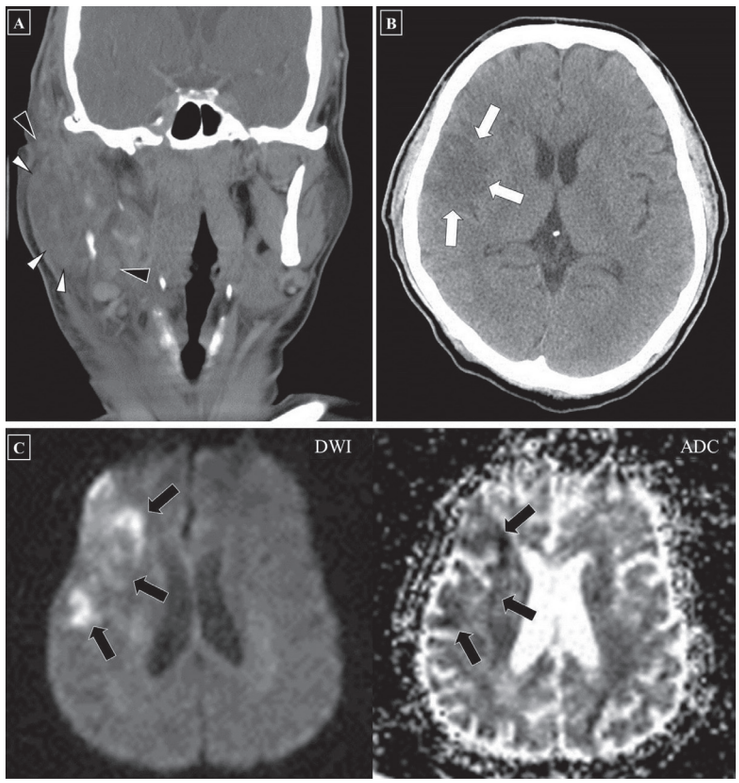

Figure 1. (A) The first contrast enhanced computed tomography revealed enhanced inflammatory swelling of right parotid gland (hollow arrowheads) and enhanced surrounding lymphadenopathies (filled arrowheads). (B) The emergent brain computed tomography revealed a hypodense area at right frontal lobe (hollow arrows). (C) Magnetic resonance imaging demonstrated an acute infarction in right frontal lobe (filled arrows), which was high-intensity signal lesion at diffusion weighted imaging (DWI) (TR/TE/excitation: 9,212/144/1) and low-intensity signal lesion at apparent diffusion coefficient mapping (ADC) (TR/TE/excitation: 9,212/144/1).

the four limbs. The bilateral Babinski plantar extensor responses were flexor. Emergent computed tomography disclosed a hypodense area at the right frontal lobe (Fig. 1B). The National Institutes of Health stroke scale (NIHSS) was scored 7. Blood examination reported protein C, protein S, anti-thrombin III, homocysteine, prothrombin time and partial thromboplastin time within normal range, but D-Dimer of 334 μg/L, which was out of normal range (0.0–324.0). Anti-nuclear antibody, anti-cardiolipin antibodies, and lupus anticoagulant were all negative. Thyroid function tests were within normal ranges. Moreover, blood amylase returned to the normal range, but leukocytosis with monocytosis, atypical lymphocytosis, thrombocytopenia, and high CRP persisted (Table 1B). In view of the underlying IM, he was prescribed oral prednisolone 10 mg twice daily and oral antiplatelet aspirin (Bokey, Yung Shin Pham Ind. Co., Taiwan) 100 mg once rather than immediate intravenous recombinant tissue plasminogen activator (rt-PA).

Two days later, muscle power in the left upper limb was still grade 0. Magnetic resonance image demonstrated acute infarction involving the right frontal lobe (Fig. 1C), and there was not any leptomeningeal or brain parenchyma enhancement by Gadolinium contrast. Magnetic resonance angiogram (MRA) illustrated all the intracranial or extracranial circulations were normal. Color-coded carotid

duplex (CCCD) and transcranial Doppler sonography (TCDS) were both unremarkable. Blood examination still showed leukocytosis with monocytosis, atypical lymphocytosis and thrombocytopenia (Table 1C), but D-dimer was normal. Transesophageal cardiac Doppler (TECD) did not demonstrate any thrombus formation in the heart. Electrocardiogram and 24-hour Holter did not demonstrate any arrthymia or other abnormality. Over the following month, rehabilitation was scheduled. Finally, the muscle power in the left upper limb was restored to grade 3, left central-type facial palsy persisted, while left hemihypesthesia subsided. Laboratory data were unremarkable (Table 1D), so the oral prednisolone was ceased. He was discharged, and received office-based rehabilitation daily. One year later, the muscle powers in all four limbs were grade 5 and left central-type facial palsy subsided. His condition was uneventful over the following three years.

DISCUSSION

Although IM is mostly associated with EBV[1], but several other organisms can also cause IM[1,7]. In the present case, acute EBV infection was little likely associated with the IM due to positive anti-EBNA, negative anti-EBV VCA IgM and positive anti-EBV VCA IgG. Because CMV IgM, mumps and HIV I/II antibody were negative, it was still not known which virus associated with the IM. However, acute ischemic stroke occurred after the pharyngitis, parotiditis and surrounding lymphadenopathies remitted. After the stroke condition went stable, leukocytosis with monocytosis, atypical lymphocytosis and thrombocytopenia were still noted (Table 1C), explicating the simultaneity of IM and the ischemic stroke.

It is known that systemic infection would increase the stroke risk by immune/inflammation[8]. Acute respiratory tract and urinary tract infections have also been reported to independently increase the risk for stroke[9]. In a population-based cohort study of a National Health Insurance database, the septicemia patients had a hazard ratio of 1.96 suffering stroke, especially a higher hazard ratio of 3.27 suffering hemorrhagic stroke, within 6 months after the infection[10]. Infection and inflammation are known to contribute to stroke by infectious burden, changes in lipid metabolism, increase plasma fibrinogen, platelet activation/aggregation, platelet lysis, hypercoagulation, alterations in endothelial function, spasm in vascular smooth muscle, atheroma instability, and subsequent plaque rupture[6-15]; besides, CMV infection would contribute to stroke by increased anticardiolipin antibodies[16]. Moreover, the preexisting stroke risk factors may influence the interaction between inflammatory cells and the surrounding resident cerebrovascular cells, thus making cerebral vessels more susceptible to inflammatory stimulation, as well as facilitating formation of atheromatous plaques in large arteries and intimal thickening with local thrombosis in smaller arterioles [12]. No wonder patients with a recent respiratory tract infection suffered more often from large-vessel athero-thrombo-embolic or cardio-embolic stroke than those without infection[6].

When the case patient suffered from acute ischemic stroke, high D-Dimer indicated the presence of thrombus formation and an abnormally high level of fibrin degradation products[13]. Hence, it was speculated that circulating monocytosis influenced the blood cholesterol metabolism, which presumably not only caused a prothrombotic state, but also triggered traditional stroke risks, such as diabetic mellitus and cigarette smoking[12]; consequently, blood hyper-coagulation led to thrombus formation in the right middle cerebral artery, resulting in right cerebral infarction despite of unremarkable MRA[12]. In addition, inflammatory markers such as leukocytes, fibrinogen, CRP and so forth are also known as independent predictors of cerebral infarction. The case patient had leukocytosis and high CRP; hence, the specific relationship between his IM and cerebral infarction was evident.

Although other causes of chronic inflammatory states might contribute to potential cerebral atherosclerosis and induce cerebral infarction, this condition could be excluded by unremarkable MRA, CCCD and TCDS in the present case; and, arrhythmia related cardiogenic thrombus could also be excluded by unremarkable electrocardiogram, 24-hour Holter and TECD. Furthermore, he did not have any neck stiffness or meningismus, and there was not any leptomeningeal or brain parenchyma enhancement during Gadolinium-enhanced magnetic resonance imaging; therefore, virus-meningitis or encephalitis was unlikely.

The disease course of the case patient was about 1.5 months, much longer than a common experience (several weeks to a month). During the course, oral corticosteroid was prescribed to relieve the autoimmune reaction triggered by an unknown virus infection; and after acute cerebral infarction, oral antiplatelet was prescribed. In conclusion, although IM is known to be self-limiting, it could contribute to acute cerebral infarction, which is a rare IM neurological complication. The sufferer with systemic infection should be informed of the stroke risk and prevention, especially younger ones without co-morbidities[10].

REFERENCES

1. Godshall SE, Kirchner JT. Infectious mononucleosis. Complexities of a common syndrome. Postgrad Med 2000;107:175–179,183–184,186.
2. McCarthy CL, McColgan P, Martin P. Acute cerebellar ataxia due to Epstein-Barr virus. Pract Neurol 2012;12:238–240.
3. Connelly KP, DeWitt LD. Neurologic complications of infectious mononucleosis. Pediatr Neurol 1994;10: 181–184.
4. Hussain RS, Hussain NA. Ataxia and Encephalitis in a Young Adult with EBV Mononucleosis: A Case Report. Case Rep Neurol Med 2013;2013:516325.
5. Fujimoto H, Asaoka K, Imaizumi T, Ayabe M, Shoji H, Kaji M. Epstein-Barr virus infections of the central nervous system. Intern Med 2003;42:33–40.
6. Paganini-Hill A, Lozano E, Fischberg G, Perez Barreto M, Rajamani K, Ameriso SF, Heseltine PN, Fisher M. Infection and risk of ischemic stroke: differences among stroke subtypes. Stroke 2003;34:452–457.
7. Melón S, Méndez S, Iglesias B, Boga JA, Rodríguez M, Fanjul JL, Méndez FJ, de Oña M. Involvement of adenovirus in clinical mononucleosis-like syndromes in young children. Eur J Clin Microbiol Infect Dis 2005;24:314–318.
8. McColl BW, Allan SM, Rothwell NJ. Systemic infection, inflammation and acute ischemic stroke. Neuroscience 2009;158:1049-1061.
9. Palm F, Urbanek C, Grau A. Infection, its treatment and the risk for stroke. Curr Vasc Pharmacol 2009;7: 146–152.
10. Lee JT, Chung WT, Lin JD, Peng GS, Muo CH, Lin CC, Wen CP, Wang IK, Tseng CH, Kao CH, Hsu CY. Increased risk of stroke after septicaemia: a population-based longitudinal study in Taiwan. PLoS One 2014;9:e89386.
11. Elkind MSV. Why now? Moving from stroke risk factors to stroke triggers. Curr Opin Neurol 2007; 20:51–57.
12. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. Stroke 2003;34:2518–2532.
13. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-Dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227–1235.
14. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. Stroke 2009;40:3443–3448.
15. Elkind MS, Ramakrishnan P, Moon YP, Boden-Albala B, Liu KM, et al. Infectious burden and risk of stroke: the northern Manhattan study. Arch Neurol 2010;67:33-38.
16. Lioger B, Debiais S, Lauvin MA, Bonnaud I, Maillot F, Ferreira-Maldent N. Anticardiolipin antibodies-associated stroke in primary CMV infection. Eur J Neurol 2013;20:e105-e106.