Int J Clin Exp Med 2018;11(9):10131-10135
www.ijcem.com /ISSN:1940-5901/IJCEM0073077

Case Report

Recurrent ischemic cerebral infarction caused by Waldenström Macroglobulinemia

Qing Wu[1*], Meizhen Liu[2*]

[1]Department of Neurology, Ningbo First Hospital, Ningbo, Zhejiang, China; [2]Department of Neurology, Ningbo Municipal Hospital of TCM, Ningbo, Zhejiang, China. [*]Equal contributors.

Received July 10, 2017; Accepted June 8, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: A 74-year-old male was admitted to hospital with recurrent unilateral limb weakness. Brain MRI demonstrated bilateral and multiple infarction lesions, but no risk factors for stroke were detected and routine examinations such as carotid artery ultrasonography, intracranial CT angiography, echocardiogram and Holter all showed negative results. The patient presented with nonspecific clinical manifestations including weight loss, fatigue and nosebleed, as well as positive laboratory results including anemia, hypoproteinemia, and abnormal albumin-globulin ratio. Further examinations were conducted and showed elevated serum IgM and plasma viscosity. Therefore, haematological disease was suspected, and the patient was ultimately diagnosed with Waldenström macroglobulinemia (WM) by bone marrow biopsy. We speculate that hyperviscosity syndrome (HVS) induced by WM may decrease blood flow and cause microcirculatory disorders, which consequently lead to the development of cerebral infarction.

Keywords: Cerebral infarction, waldenström macroglobulinemia, hyperviscosity syndrome

Introduction

Waldenström macroglobulinemia (WM) is diagnosed by the presence of a lymphoplasmacytic infiltration in the bone marrow and serum monoclonal IgM of any amount [1]. Approximately 10% to 30% of patients with WM present with hyperviscosity syndrome (HVS) [2, 3]. HVS can cause a series of complicated physiopathological changes which may lead to vascular thrombosis. We describe a patient who presented with no common cerebrovascular risk factors and suffered from recurrent cerebral infarctions.

Case report

A 74-year-old man arrived at our emergency room with a one-day history of weakness in his left limbs. He complained of sudden weakness, leading to an inability to walk. He also mentioned paresthesia of his left limbs, denied speech disorder, and disturbances in urination and defecation functions. There was no history of hypertension, diabetes, hyperlipemia, coronary heart disease, or other serious diseases, other than a sudden and transient onset of weakness in his right limbs seven days prior to his initial consultation. He recovered completely several minutes later from this previous episode and was treated at the local hospital with aspirin without hospitalization. The patient also reported a weight loss of five kilograms and suffered from fatigue, blurred vision, and intermittent nosebleed for the past three months.

Neurological examination revealed 4/5 of muscle strength, diminished feeling of pain and warmth in the patient's left limbs, Babinski sign was also positive in his left lower extremity. In addition, no other nervous system abnormalities were detected. Brain MRI showed acute infarction in the right frontal and parietal lobes, subacute infarction in the left parietal lobe, and old infarction in the right cerebellum (**Figure 1**).

To explore the etiology of the multiple and recurrent ischemic cerebral infarctions, we performed carotid artery ultrasonography, carotid artery and intracranial CT angiography, echocardiogram, and 24-hour Holter cardiac rhythm monitoring, but all the above examinations revealed negative findings. Transcranial Doppler (TCD) with saline contrast medium also showed

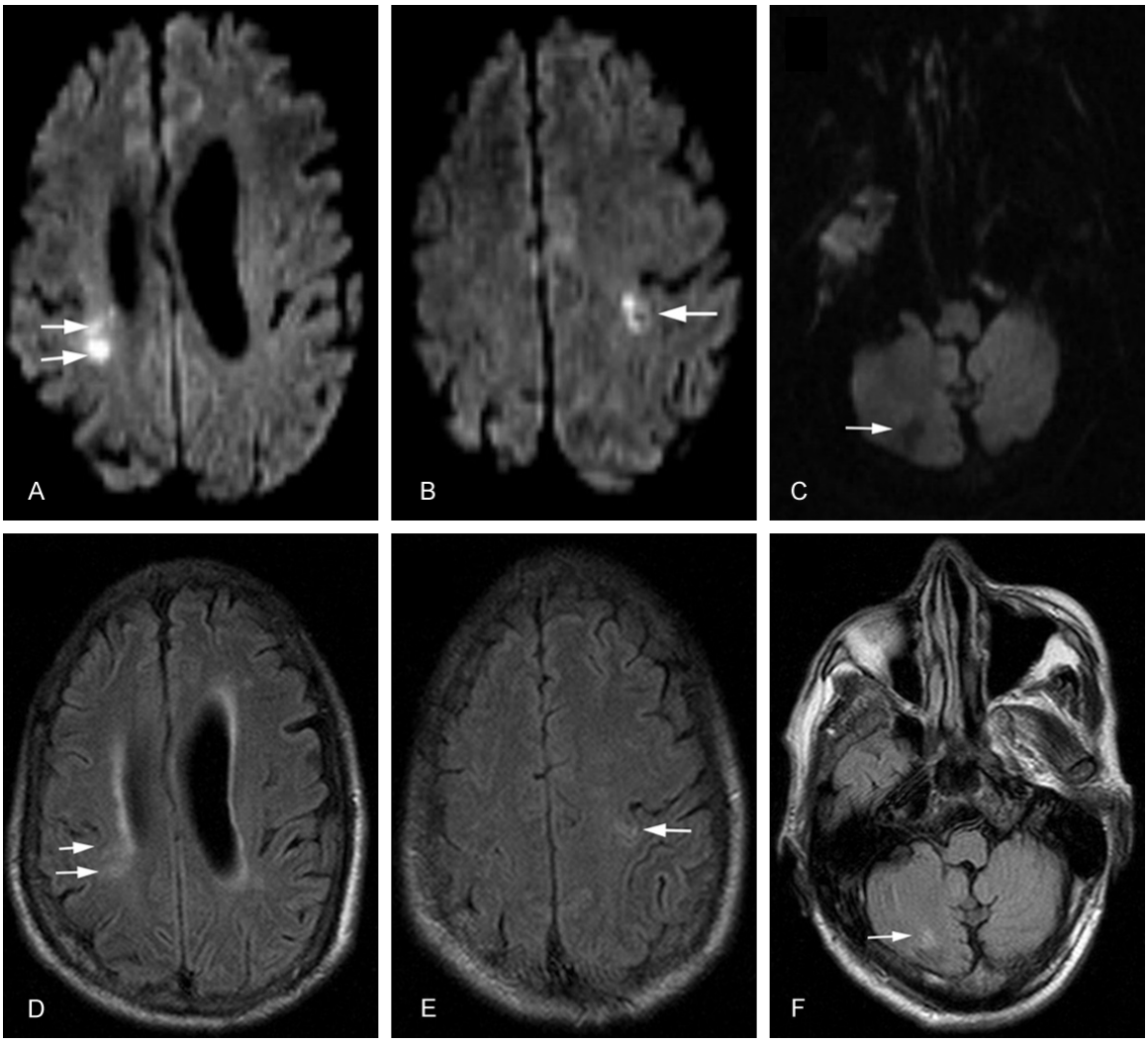

Figure 1. Brain MRI imaging (A). MRI diffusion-weighted imaging sequence demonstrates significant hyperintensities in the right frontal and parietal lobe (acute infarction). (B) MRI diffusion-weighted imaging sequence demonstrates slight hyperintensity in left parietal lobe(subacute infarction). (C) MRI diffusion-weighted imaging sequence reveals hypointensity in the right cerebellum(old infarction). (D-F) MRI T2/fluid-attenuated inversion recovery sequence shows mild hyperintensities in corresponding locations of lesion.

no valuable results (no microembolic signal detected with or without valsalva maneuver).

Basic laboratory tests revealed as the following: hemoglobin 8 g/dl, red blood cell count 2.95×10^{12}/L, fibrinogen 5.9 g/dl (reference value: 2.0-4.7 g/dl), total protein 89.8 g/dl, albumin 29.3 g/dl (reference value: 40.0-55.0 g/dl), globulin 60.5 g/dl, albumin-globulin ratio (AGR) was 0.48 (reference value: 1.2-2.4). Since albumin and globulin are major serum proteins as well as representative indicators of systemic inflammation [4], the abnormal albumin-globulin ratio and anemia were highly indicative of tumor, hepatopathy, as well as rheumatic and hematologic diseases. Therefore, further laboratory tests were performed: liver function and tumor markers were within normal limits, while rheumatic test, hepatitis, syphilis, and HIV tests were negative. Other test results were as follows: serum immunoglobulin IgG 1710 mg/dl (reference value: 751-1560 mg/dl), IgM 4940 mg/dl (reference value: 46-304 mg/dl), immunofixation electrophoresis IgM k type, blood KAP light chain 7520 mg/dl (reference value: 629-1350 mg/dl), blood LAM light chain 231 mg/dl (reference value: 269-638 mg/dl), KAP/LAM 32.55 (reference value: 1.47-2.95), M-protein positive (40.1%), ESR135 mm/h, and

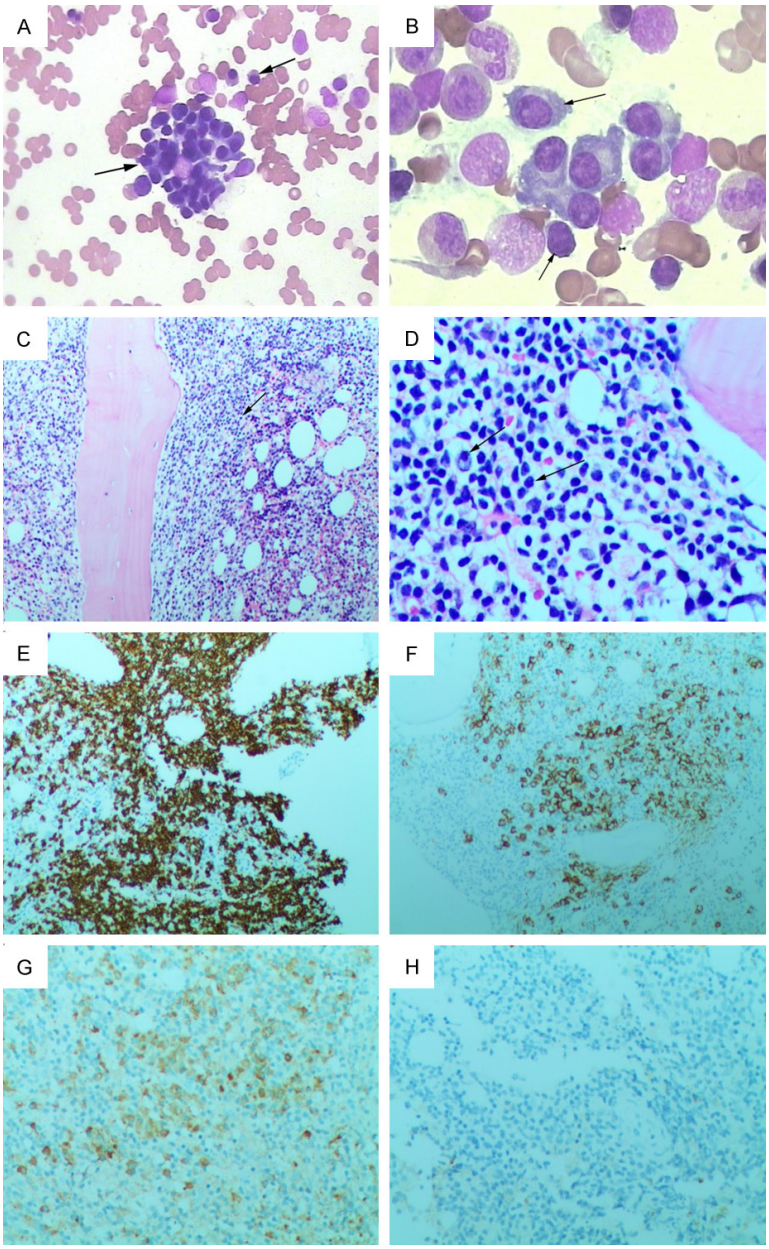

Figure 2. Bone marrow cytologic and pathologic findings. A, B. Numerous plasma cells and some lymphoplasmacytoid cells could be seen (bone marrow cytology, low and high magnification). C, D. The diffuse hyperplasia of small lymphocytes, plasmacytoid lymphocytes and plasma cells, with their nucleus deeply stained (bone marrow pathology, hematoxylin & eosin stain 100× and 400×). E. CD20 positive (100×). F. CD138 positive (100×). G. kappa positive (200×). H. lambda negative (200×).

plasma viscosity 4.88 mPas (reference value: 1.26-1.66).

As we evaluated the patient's clinical symptoms (weight loss, fatigue, nose-bleeding) and laboratory examinations (anemia, hypoproteinemia, elevated ESR, serum IgM and KAP/LAM), haematological diseases (especially multiple myeloma) were strongly considered. X-ray was conducted and revealed that the patient was negative for osteolytic bone lesion, while bone marrow routine test indicated that plasma cells and lymphoplasmacytoid cells were detected. Bone marrow biopsy indicated diffuse hyperplasia of small lymphocytes, plasmacytoid lymphocytes and plasma cells, the immunophenotype was IgM(+), CD19(+), CD20(+), CD5(-), CD10(-), and CD23(-), and the plasmacytoid differentiated cells had the following markers: CD138(+), CD38(+), kappa(+), lambda(-) (**Figure 2**). According to the above results, the final diagnoses were determined to be multiple cerebral infarctions and WM. In addition to secondary prevention for stroke (aspirin and atorvastatin), further treatment requiring chemotherapy was initiated at a local hospital after discharge. At follow up over one and a half years later, the patient experienced no recurrence of stroke, and his serum IgM and plasma viscosity decreased to 1860 mg/dl and 1.86 mPas, respectively.

Discussion

Cerebral infarction is a major cause of disabilities, and the etiology can be divided into five subtypes according to the Trial of Org 10172 in Acute Stroke Treatment criteria (TOAST): (1) large artery atherosclerosis, (2) cardioembolism, (3) small artery occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology [5]. In this case, brain MRI revealed multiple infarctions involving acute, subacute and old lesions, suggesting recurrent infarction (the previous tran-

sient ischemic attack was suspected to be a subacute infarction in the left parietal lobe). Routine examinations excluded common causes of stroke and cryptogenic stroke was considered. Meanwhile, the nonspecific test results such as anemia, hypoproteinemia, and abnormal albumin-globulin ratio caught our attention and subsequent tests were performed. Ultimately, elevated IgM and HVS were highly indicative of hematopathy, and WM was diagnosed by bone marrow biopsy. As a haematological disease, WM may have a close relationship with stroke.

WM is defined as lymphoplasmacytic lymphoma (LPL) associated with monoclonal immunoglobulin M (IgM), and the clinical presentations can manifest as nonspecific symptoms: fatigue, weight loss, hepatomegaly, splenomegaly, anemia, or present as peripheral neuropathy, cryoglobulinemia, and HVS [6, 7]. The typical immunophenotype is positive for CD19, CD20, CD22, CD25, CD27, CD38, CD79a, FMC7, surface/cytoplasmic IgM, and negative for CD5, CD10, CD11c, CD23, and CD103 [1, 6, 8].

HVS is a clinical feature in a portion of patients with WM, and it could manifest as neurologic changes in patients with IgM concentration above 3000 mg/dl and serum viscosity above four mPas. The neurological presentation of HVS generally includes dizziness, sight blur, headache, deafness and papilledema, while significantly elevated serum viscosity (especially > 4.0 mPas) can lead to vasoocclusive events [9]. To our knowledge, cerebral ischemic stroke mainly relating to HVS caused by WM has seldomly been reported. In this case, we speculate that the abnormal monoclonal IgMs may wrap erythrocytes and reduce the repulsive force of negative charge on the surface of erythrocytes. Consequently, the erythrocytes aggregate in abnormal ways, resulting in slow blood flow and the increase of resistance to flow. As a result of this process, severe microcirculatory disorders appear, which then cause histanoxia and capillary wall destruction that finally lead to a series of symptoms of vascular thrombosis. It has been reported that nonspecific IgM deposition, autoimmune phenomena and direct cellular infiltration of the central neuraxis are also likely to be causes for neurological impairment in WM patients, but these neurological impairments principally appear as white matter and peripheral nerve demyelination [9], which was not the case in this patient. Additionally, some WM patients present with cryoglobulinemia which can also result in vascular thrombosis (generally as vasculitis). Nonetheless, the clinical manifestations of cryoglobulinemia, such as arthralgia, purpura, mucosa ulcer, renal dysfunction were not observed in this case [10].

In this case, when we combined the patient's clinical manifestations, laboratory results, and brain imaging, we discovered a series of constitutional symptoms and markedly elevated serum IgM as well as HVS. The patient also lacked evidence of white matter, peripheral nerve demyelination and cryoglobulinemia, and had negative results for common stroke etiologies. It was reasonable to speculate that the recurrent and multiple cerebral ischemic strokes were probably induced by HVS owing to WM.

In conclusion, WM should also be taken into account when treating cryptogenic stroke patients, especially if some suggestive symptoms (such as blurred vision and nosebleed) and laboratory results (such as anemia, hypoproteinemia, and abnormal albumin-globulin ratio) accompany the patient. Early treatment and prevention are essential for patients and further studies examining the pathophysiological mechanism of WM and stroke are needed in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Meizhen Liu, Department of Neurology, Ningbo Municipal Hospital of TCM, 819 LiYuan North Road, Haishu District, Ningbo 315000, Zhejiang, China. Tel: +86-547-87089069; Fax: +86-547-87089069; E-mail: xkfyallen@163.com

References

[1] Abeykoon JP, Yanamandra U and Kapoor P. New developments in the management of waldenstrom macroglobulinemia. Cancer Manag Res 2017; 9: 73-83.

[2] Stone MJ and Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. Blood 2012; 119: 2205-2208.

[3] Mehta J and Singhal S. Hyperviscosity syndrome in plasma cell dyscrasias. Semin Thromb Hemost 2003; 29: 467-471.
[4] Oki S, Toiyama Y, Okugawa Y, Shimura T, Okigami M, Yasuda H, Fujikawa H, Okita Y, Yoshiyama S, Hiro J, Kobayashi M, Ohi M, Araki T, Inoue Y, Mohri Y and Kusunoki M. Clinical burden of preoperative albumin-globulin ratio in esophageal cancer patients. Am J Surg 2017; 214: 891-898.
[5] Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL and Marsh EE 3rd. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. toast. trial of org 10172 in acute stroke treatment. Stroke 1993; 24: 35-41.
[6] Yun S, Johnson AC, Okolo ON, Arnold SJ, McBride A, Zhang L, Baz RC and Anwer F. Waldenstrom macroglobulinemia: review of pathogenesis and management. Clin Lymphoma Myeloma Leuk 2017; 17: 252-262.
[7] Gertz MA. Waldenstrom macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. Am J Hematol 2017; 92: 209-217.
[8] Lin P and Medeiros LJ. Lymphoplasmacytic lymphoma/waldenstrom macroglobulinemia: an evolving concept. Adv Anat Pathol 2005; 12: 246-255.
[9] Baehring JM, Hochberg EP, Raje N, Ulrickson M and Hochberg FH. Neurological manifestations of Waldenstrom macroglobulinemia. Nat Clin Pract Neurol 2008; 4: 547-556.
[10] Cacoub P, Comarmond C, Domont F, Savey L and Saadoun D. Cryoglobulinemia vasculitis. Am J Med 2015; 128: 950-955.