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Case Report

Hyperhomocysteinemia-related lung disease and hemolytic anemia with bone marrow features masquerading as myelodysplasia

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Abstract: Hyperhomocysteinemia is linked to TMA-related clinical symptoms such as apparent thromboembolism, microangiopathic hemolytic anemia (MAHA), and various types of end-organ damage due to microvascular thrombi; this is because high plasma levels of homocysteine impair the vascular endothelium. However, the association between hyperhomocysteinemia and pulmonary involvement is unclear. Here, we describe a 63-year-old male who was hospitalized with respiratory failure and MAHA with MDS-like features in the bone marrow. Plasma homocysteine levels were elevated significantly with 199.4 μmol/L (reference: 6.3-18.9) due to a homozygous (T/T) polymorphism for the 677C>T mutation within the *MTHFR* gene associated with chronic alcoholism-induced folate deficiency. Pulmonary lesions showed ground-glass opacity and there was pleural effusion. The patient was managed successfully with a combination of folate/mecobalamin supplementation, plasma exchange, and a methylprednisolone pulse, followed by oral prednisolone. Clinical symptoms, lung disease, MAHA, and bone marrow abnormalities improved as plasma homocysteine levels normalized.

Keywords: Hyperhomocysteinemia, thrombotic microangiopathy, methylenetetrahydrofolate reductase, lung disease, myelodysplasia

Introduction

Hyperhomocysteinemia is a risk factor for thromboembolism because high plasma levels of homocysteine damage the vascular endothelium [1, 2]. It also triggers thrombotic microangiopathy (TMA)-like features, characterized by the appearance of increased numbers of schistocytes in the peripheral blood [3]. TMA is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and microvascular thrombi that cause end-organ damage [4]. However, the association between hyperhomocysteinemia and pulmonary involvement (diffuse lung disease and pulmonary arterial hypertension, with or without thromboembolism) remains unclear [5-7]. By contrast, hyperhomocysteinemia has been reported in cases of myelodysplastic syndrome (MDS) [8]. Hyperhomocysteinemia is caused by a combination of nutritional deficiency, particularly vitamin B6, vitamin B12, or folate, and a 677C>T polymorphism (T/T type) of the methylenetetrahydrofolate reductase *(MTHFR*) gene [9-12]. Here, we report a rare case of hyperhomocysteinemia-related lung disease in an elderly patient with MAHA triggered by chronic alcoholism-induced folate deficiency associated with T/T type polymorphism of the *MTHFR* C677T gene; the patients showed bone marrow characteristics mimicking MDS. The patient was treated successfully with folate/mecobalamin supplementation and plasma exchange followed by prednisolone administration.

Case report

A 63-year-old male patient visited the emergency clinic with palpitations on exertion. He had a history of alcoholism and a cerebral infarct at the left basal ganglia, which caused hemiparesis 3 years earlier. The following data were obtained on admission: height, 173 cm; weight,

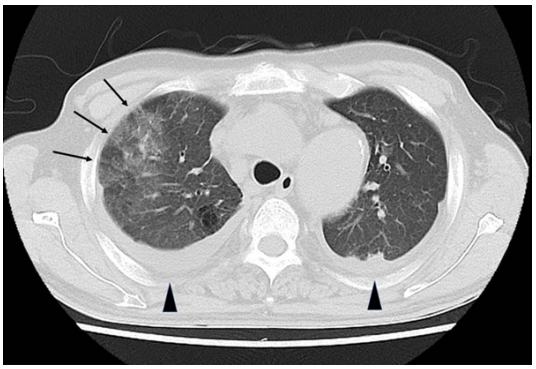

Figure 1. Lung CT shows diffuse ground-glass opacification, predominantly in the upper region of the right lung (arrows), associated with pleural effusion in both lungs (arrow heads). No infectious or autoimmune cause was identified.

63.2 kg; temperature, 36.9°C. He was alert, but respiratory failure required oxygenation (5 L/min) to maintain SpO_2 at 97%. Under these conditions, blood pressure was 111/79 mmHg; heart rate, 108/min (with no arrhythmia); and respiratory rate, 22/min. Neither rales nor heart murmurs were audible on chest auscultation. Chest computed tomography (CT) revealed pleural effusion and ground-glass opacity in the right upper lung fields (**Figure 1**), but neither infectious nor autoimmune respiratory disease was identified. Contrast-enhanced CT showed no evidence of pulmonary thromboembolism. Laboratory data were as follows: WBC 5,400/μL (reference: 3,000-8,500), Hb 6.2 g/dL (13-17), MCV 112.2 fL (83-100), platelet count 121 K/μL (150 K-360 K); reticulocyte count 11‰ (3-11), serum CRP 0.61 mg/dL (<0.29), AST 169 U/L (13-37), ALT 88 U/L (8-45), LDH 4,452 U/L (122-228) with a LDH isozyme 1 and 2 dominant pattern, indirect bilirubin 2.68 mg/dL (<0.5) and haptoglobin 2 mg/dL (>58). Renal function was normal. A direct Coombs test was negative, and a peripheral blood smear showed increased numbers of schistocytes (**Figure 2A**), which is indicative of TMA-induced MAHA. Serum vitamin B12 levels were normal with 339 pg/mL (reference: 233-914), while folate levels were low with 2.7 ng/mL (3.6-12.9). Coagulation data were as follows: PT-INR 1.43 (0.9-1.1), APTT 40.7 sec (control: 28.2), fibrinogen 136 mg/dL (200-400), FDP 7.2 μg/mL (<2.5) and D-dimer 3.4 μg/mL (<1.0). Other data were as follows: plasma homocysteine 199.4 μmol/L (6.3-18.9), ADAMTS13 activity 37% (25-50% defined as a mild decrease); complement C3 44 mg/dL (80-140), C4 15.8 mg/dL (11-34); CH50 21 U/mL (30-45) and sIL-2R 322 U/L (122-496). Anti-nuclear antibodies, lupus anticoagulant, and other autoimmune antibodies were negative. There were no renal failure/neurologic symptoms. Bone marrow was normocellular, with significant erythroid hyperplasia (total erythroid 40%, with 20% pro-normoblasts) and an M/E ratio of 0.98 in association with florid erythroid dysplasia. No increase of non-erythroid blasts was noted (**Figure 2B**). The bone marrow karyotype was 46, XY (20/20). Under the 2016 WHO classification, we made a diagnosis of MDS [13]. Eventually, he was tested for *MTHFR* gene polymorphism; the patient was homozygous (T/T) for the *MTHFR* 677C>T gene variant.

Considering his poor general condition, he received prophylactic antibiotics (CTRX) treatment. On the 5th hospital day, a plasma homocysteine assay conducted by an external laboratory showed a significantly high value; therefore, he received a combination of oral folate (15 mg/day)/mecobalamin (1000 μg/day). In addition, he received plasma exchange (40 U/day) with methylprednisolone pulse (500 mg/day) for three successive days. This was followed by oral prednisolone (initial dose, 60 mg/day [approximately 0.95 mg/kg/day], followed by tapering) (**Figure 3**). As shown, along with rapid decline of plasma levels of homocysteine, clinical symptoms such as lung disease and MAHA improved within 2-3 weeks after the interventions. The patient became able to maintain SpO_2 >95% without oxygenation, with normalized plasma FDP/D-dimer, after 7 days. MAHA-related pancytopenia also improved in association with serum LDH down from 4,452 U/L to 321 U/L in 2 weeks. Plasma homocysteine levels normalized after 3 weeks. When his general condition stabilized, the patient received cardiac catheter examination, which suggested no pulmonary arterial hypertension (PAH). Also, no thromboembolism was found in pulmonary vessels on repeated contrast-enhanced CT. Furthermore, repeat bone marrow examination at week 7 of treatment, found no features of MDS.

Discussion

The hyperhomocysteinemia in our case was thought to be due to the combined effect of alcoholism-induced folate deficiency and a

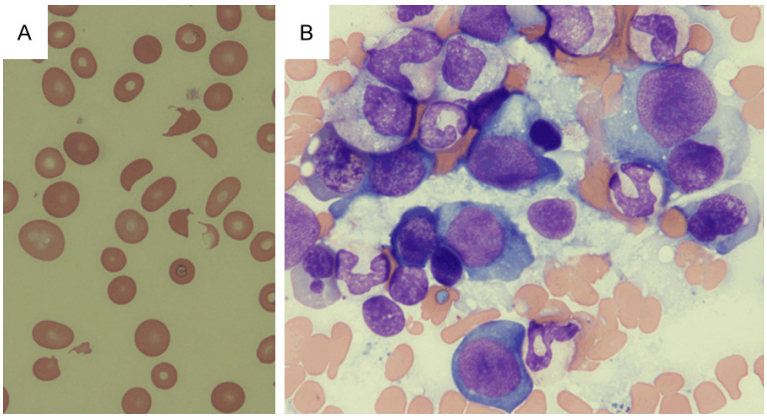

Figure 2. A. Peripheral blood film shows schistocytes on the smear (original magnification ×1,000). B. Bone marrow analysis reveals pronormoblast-dominant erythroid hyperplasia associated with florid erythroid dysplasia, which was diagnosed initially as MDS (original magnification ×1,000).

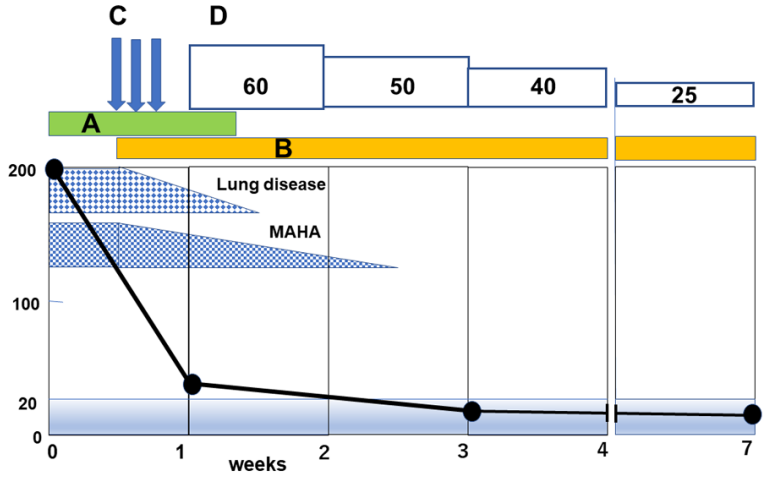

Figure 3. Clinical course of the patient. The bold black line graph indicates plasma levels of homocysteine, which declined rapidly during the first week and remained within the normal range between weeks 3-7. Clinical symptoms such as lung disease and MAHA improved within 2-3 weeks after the interventions. Units on the vertical axis = μmol/L. Therapy comprised of (A) intravenous CTRX (1 g/day); (B) oral folic acid (15 mg/day) and mecobalamin (1000 μg/day); (C) plasma exchange (40 U/day for 3 days) with methylprednisolone pulse (500 mg/day ×3 days); and (D) oral prednisolone (starting dose 60 mg/day, tapered weekly).

homozygous (T/T) type *MTHFR* gene polymorphism. Nutritional deficiency, particularly vitamin B6, vitamin B12, and folate, due to chronic alcohol intake could disrupt the methionine cycle, resulting in high plasma levels of homocysteine [14, 15]. The cerebral infarct that occurred 3 years earlier was also assumed to be related to hyperhomocysteinemia [16], although homocysteine levels were not tested at that time. However, this time, the clinical symptoms of lung disease were thought to be related to hyperhomocysteinemia. As hyperhomocysteinemia-related lung disease, primary PAH, chronic thromboembolic pulmonary hypertension (CTEPH) as well as diffuse lung disease (DLD) have been described (**Table 1**). In association with hyperhomocysteinemia, TMA might have caused vasoconstriction, vascular smooth muscle cell proliferation, and microthrombus formation in the lungs; the damaged vascular endothelial cells in the pulmonary vessels may then lead to increased permeability of pulmonary capillaries, resulting in the diffuse ground-glass opacification and nodular images [5-7, 17]. Thus, we assumed that the lung disease was closely linked to high plasma homocysteine levels because we ruled out other causes such as infectious and/or autoimmune diseases; also, FDP/D-dimer levels which were high at onset normalized together with clearance of lung shadows in 7 days. In addition, although we first suspected that the high plasma homocysteine level was due, at least in part, to MDS (as described by Cortelezzi [8]), the later disappearance of MDS-like bone marrow features associated with improved homocysteine and folate levels indicates that initial bone marrow findings were masquerading as MDS due to hyperhomocysteinemia.

The patient was treated successfully with a combination of folate/mecobalamin supplementation, plasma exchange, and prednisolone. Plasma exchange has been proposed for the management of conditions associated with TMA [4], although hyperhomocysteinemia-related lung disease is not included as an indication for this therapeutic measure [4]; fortu-

Table 1. Hyperhomocysteinemia-related lung disease

Lung disease	Clinical characteristics/Diagnostic clues	reference
Primary PAH	Fatigue, shortness of breath, High PAP, No evidence of thrombotic material within the PA, Primary PAH was noted in 8/18 (hyperhomocysteinemia) vs. 3/36 (control) (P=0.005) [5]	[5]
Chronic thromboembolic PAH (CTEPH)	Dyspnea, exercise intolerance, High PAP, Mismatched perfusion defects on ventilation/perfusion scan Detection of thrombotic material within the PA by contrast CT images	[21-23]
Diffuse lung disease (DLD)	Chronic wet cough, respiratory failure, HRCT shows diffuse interstitial pneumonia, pulmonary consolidation, with or without pleural effusions. PAH was associated with 3/4 and 6/6 patients described in [6, 7], respectively. No thromboembolism was detected	[6, 7]

Abbreviations: PA = pulmonary artery, PAH = pulmonary arterial hypertension, PAP = pulmonary artery pressure, HRCT = High-resolution computed tomography.

nately, in our case, plasma exchange was useful in reducing the levels of plasma homocysteine rapidly. Furthermore, we assume that prednisolone might have worked by repairing systemic vascular endothelial damage including pulmonary vessels, thereby improving lung disease and MAHA.

Hyperhomocysteinemia is caused by folate/vitamin B12 deficiency [3, 18] (with or without the homozygous (T/T) 677C>T *MTHFR* gene) [9-12], cystathionine-β-synthase gene mutations [19], or a combination of these. In our case, the *MTHFR* gene (T/T) variant might have played a major role in causing exceedingly high plasma homocysteine levels. Increased plasma levels of homocysteine are generally defined as moderate (15-30 μmol/L), intermediate (30-100 μmol/L), or marked (>100 μmol/L) [20]. To date, reported plasma homocysteine levels in cases of pulmonary/hematological diseases are as follows: 20.4 μmol/L [21], >50.0 μmol/L [10], 70 μmol/L [22], 50-250 μmol/L [23], and 12-43 μmol/L [8]. The clinical symptoms in our case (lung disease, MAHA, and MDS-like bone marrow features) were thought to be due to significantly high plasma homocysteine levels (199.4 μmol/L).

In summary, plasma homocysteine, vitamin B12, and folate levels should be assessed when a patient presents with TMA-like features associated with increased numbers of schistocytes in the blood, MAHA and lung disease. Additionally, genetic analysis of the *MTHFR* C677T polymorphism is essential. Since cases of CTEPH complicated by hyperhomocysteinemia has been reported [21, 23], close follow-up of this patient is planned after discharge from hospital.

Disclosure of conflict of interest

None.

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References

[1] Esse R, Barroso M, Tavares de Almeida I and Castro R. The contribution of homocysteine metabolism disruption to endothelial dysfunction: state-of-the-art. Int J Mol Sci 2019; 20: 867.

[2] Salvagno GL, Pavan C and Lippi G. Rare thrombophilic conditions. Ann Transl Med 2018; 6: 342.

[3] Yamanishi M, Koba S, Jo T, Kotera T and Imashuku S. Thrombotic microangiopathy-like hemolysis in vitamin B12 deficiency-related macrocytic anemia. Clin Lab 2018; 64: 639-643.

[4] Adamski J. Thrombotic microangiopathy and indications for therapeutic plasma exchange. Hematology Am Soc Hematol Educ Program 2014; 2014: 444-449.

[5] Arroliga AC, Sandur S, Jacobsen DW, Tewari S, Mustafa M, Mascha EJ and Robinson K. Association between hyperhomocysteinemia and primary pulmonary hypertension. Respir Med 2003; 97: 825-829

[6] Liu J, Peng Y, Zhou N, Liu X, Meng Q, Xu H and Zhao S. Combined methylmalonic acidemia and homocysteinemia presenting predominantly with late-onset diffuse lung disease: a case series of four patients. Orphanet J Rare Dis 2017; 12: 58.

[7] Tang XL, Yang HM, Liu H, Xu H, Zhou CJ, Li HM, Zhao SY and Liu JR. Clinical analysis of methylmalonic acidemia and hyperhomocysteinemia with diffuse lung disease as an initial or main presentation. Zhonghua Er Ke Za Zhi 2019; 57: 620-624.

[8] Cortelezzi A, Fracchiolla NS, Bamonti-Catena F, Motta M, Cighetti G, Carrabba M, Cavalca V, Maiolo AT and Lambertenghi Deliliers G. Hy-

perhomocysteinemia in myelodysplastic syndromes: specific association with autoimmunity and cardiovascular disease. Leuk Lymphoma 2001; 41: 147-150.
[9] Fujimura H, Kawasaki T, Sakata T, Ariyoshi H, Kato H, Monden M and Miyata T. Common C677T polymorphism in the methylenetetrahydrofolate reductase gene increases the risk for deep vein thrombosis in patients with predisposition of thrombophilia. Thromb Res 2000; 98: 1-8.
[10] Liu F, Silva D, Malone MV and Seetharaman K. MTHFR A1298C and C677T polymorphisms are associated with increased risk of venous thromboembolism: a retrospective chart review study. Acta Haematol 2017; 138: 208-215.
[11] Al-Batayneh KM, Zoubi MSA, Shehab M, Al-Trad B, Bodoor K, Khateeb WA, Aljabali AAA, Hamad MA and Eaton G. Association between MTHFR 677C>T polymorphism and vitamin B12 deficiency: a case-control study. J Med Biochem 2018; 37: 141-147.
[12] Masuda K and Imashuku S. Venous thromboembolism associated with hyperhomocysteinemia, homozygosity for the methylenetetrahydrofolate reductase 677C>T gene variant, and secondary polycythemia. Blood Coagul Fibrinolysis 2020; 31: 270-273.
[13] Boddu P, Benton CB, Wang W, Borthakur G, Khoury JD and Pemmaraju N. Erythroleukemia-historical perspectives and recent advances in diagnosis and management. Blood Rev 2018; 32: 96-105.
[14] Sanvisens A, Zuluaga P, Pineda M, Fuster D, Bolao F, Juncà J, Tor J and Muga R. Folate deficiency in patients seeking treatment of alcohol use disorder. Drug Alcohol Depend 2017; 180: 417-422.
[15] Cravo ML and Camilo ME. Hyperhomocysteinemia in chronic alcoholism: relations to folic acid and vitamins b6 and b12 status. Nutrition 2000; 16: 296-302.
[16] Anniwaer J, Liu MZ, Xue KD, Maimaiti A and Xiamixiding A. Homocysteine might increase the risk of recurrence in patients presenting with primary cerebral infarction. Int J Neurosci 2019; 129: 654-659.
[17] Grangé S, Bekri S, Artaud-Macari E, Francois A, Girault C, Poitou AL, Benhamou Y, Vianey-Saban C, Benoist JF, Châtelet V, Tamion F and Guerrot D. Adult-onset renal thrombotic microangiopathy and pulmonary arterial hypertension in cobalamin C deficiency. Lancet 2015; 386: 1011-1012.
[18] Li WX, Cheng F, Zhang AJ, Dai SX, Li GH, Lv WW, Zhou T, Zhang Q, Zhang H, Zhang T, Liu F, Liu D and Huang JF. Folate deficiency and gene polymorphisms of MTHFR, MTR and MTRR elevate the hyperhomocysteinemia risk. Clin Lab 2017; 63: 523-533.
[19] Shang K, Li H and Luo X. Cerebral venous sinus thrombosis due to hyperhomocysteinemia with cystathionine-β-synthase (CBS) gene mutation. Medicine (Baltimore) 2019; 98: e14349.
[20] Hankey GJ and Eikelboom JW. Homocysteine and vascular disease. Lancet 1999; 354: 407-413.
[21] Low LYH, Sia CH, Tay EL and Loh JPY. Chronic thromboembolic pulmonary hypertension and homocysteinaemia. QJM 2018; 111: 121-122.
[22] Ruggeri P, Lo Bello F, Nucera F, Gaeta M, Monaco F, Caramori G and Girbino G. Hereditary hyperhomocysteinemia associated with nephrotic syndrome complicated by artery thrombosis and chronic thromboembolic pulmonary hypertension: a case report. Monaldi Arch Chest Dis 2017; 87: 880.
[23] Ogawa S, Katayama T, Kaikita K, Tsukamoto M, Yamamoto E, Yamamuro M, Tanaka T, Tsujita K, Kojima S, Tayama S, Hokimoto S, Yamabe H, Indo Y, Endo F, Matsubara H and Ogawa H. Chronic thromboembolic pulmonary hypertension complicated with homocystinuria. Intern Med 2014; 53: 2605-2608.