Early Onset Predominantly Diffuse Lung Disease in an Infant of Combined Methylmalonic Acidemia With Hyperhomocysteinemia Cobalamin C Type

E levated blood methylmalonic acid (MMA) levels combined with elevated homocysteine is called combined methylmalonic acidemia with hyperhomocysteinemia [1,2]. It is found that MMA may damage the central nervous system, retina, liver, kidneys and blood cells. It also causes macular coloboma, thrombotic microangiopathy [3], and sometimes pulmonary arterial hypertension (PAH) [4,5], but an association between combined methylmalonic acidemia with hyperhomocysteinemia and diffuse lung disease (DLD) has rarely been reported in infants [6].

A 7-month-old boy was admitted with complaints of pallor for 30 days. It was followed by cough 8-10 days later. Personal history showed delayed motor development. The child was hospitalized in a local hospital for respiratory distress. Investigations showed white blood cell count of 9.78 X10^9/L, hemoglobin of 6 g/L, platelet count 319X10^9/L, and reticulocytes of 9%. High resolution computed tomography (HRCT) scan of the lungs revealed diffuse lesions in both lungs. Cytomegalovirus DNA detection revealed 5.08x10^5 copies/mL in sputum. Injection meropenem, azithromycin, voriconazole and ganciclovir were administered. In spite of the above treatment, child continued to have progressively worsening respiratory difficulty. He was intubated transferred to our hospital.

We added trimethoprim-sulfamethoxazole with a possibility of Pneumocystis carinii infection. Further investigations were non-contributory for bacterial, fungal and tuberculosis infection, and liver and renal function tests were
within normal limits. Serum erythropoietin level was >750.0 mIU/mL, vitamin B12 >1000 pg/mL and folic acid >24.0 ng/mL. The morphology of red blood cell of the peripheral blood, and bone marrow aspiration had no abnormalities. Thoracoscopic lung biopsy was performed and pathology showed alveolar septum widened with local atelectasis and pulmonary arteriolar thickening. Further blood tests and tandem mass spectrometry revealed increased homocysteine levels (95.9 µmol/L; normal: 10-40 µmol/L) and highly elevated MMA (0.2598; normal levels: 0.001). We performed a whole exome sequencing and confirmed a compound enzyme deficiency and greater accumulation of metabolic waste adding to a poor prognosis and higher mortality [3]. Treatment with hydroxycobalamin and betaine has been shown to be efficient in MMACHC. Hydroxycobalamin is considered to be the only form of cobalamin to be beneficial in patients with MMACHC [1]. A possible reason of slow improvement could be non-availability of hydroxycobalamin; however, beneficial effect with cyanocobalamin is also reported [6].

MMA patients have been reported to have pulmonary vascular embolism [6]. Our patient also had hematologic abnormalities; however, there was no obvious abnormality in the peripheral blood smear, and no micro-thrombotic change in the lung biopsy. Although the elder brother did not have a definite diagnosis, MMACHC was the most likely candidate considering his medical history and his brother’s final diagnosis suggesting that genetic background plays an important role in the age of onset and phenotype of the disease.

In summary, our report suggests that MMACHC should be considered as a potential cause of DLD. Early recognition, diagnosis and treatment of MMACHC defect are important, especially in early-onset cases.

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