To the Editor,

Cyanosis in an apparently healthy newborn baby may be caused by hemoglobin (Hb) variants associated with the formation of methemoglobin. Such Hb variants are collectively known as M Hbs [1]. Hb M-Iwate [alpha2 87(F8) His>Tyr, HBA2:c.262C>T] is one of the Hb variants associated with methemoglobinemia [2].

Many Hb variants have been reported so far from Turkey [3,4,5]. We report herein a newborn baby from Bursa, Turkey, with methemoglobinemia and (pseudo) cyanosis having Hb M-Iwate as the underlying cause. To our knowledge, this is only the second report of Hb M-Iwate from Turkey, and more than four decades have passed since its first observation in Turkey in a 21-year-old male by Ozsoyulu [6]. In addition, our case represents the first case of Hb M-Iwate from Turkey identified through genetic analysis of the α-globin chain gene (HBA).

The boy, born at term to a 32-year-old mother, was noted to be cyanotic immediately after birth. He had findings of dyspnea and he received oxygen by hood.

In the family history, the mother had history of cyanosis, particularly in the peroral area, and was otherwise healthy. In addition, the maternal grandfather and his mother, who had migrated from Thessaloniki (Greece), also had a history of cyanosis.

In venous blood gas analysis, pH was 7.43, pCO₂ concentration was 13.5% (normal: <1.5%). Complete blood oxygen did not result in an increase of the measured SpO₂. The oxygen saturation (SpO₂), measured by pulse oximeter, was between 50% and 60%. Administration of oxygen by hood was ineffective in improving the SpO₂.

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count testing (Table 1) and echocardiographic examination were both normal.

In the follow-up of the case, findings of dyspnea resolved by the 3rd postnatal day, although cyanosis persisted. The baby was discharged on the 4th day in good condition.

Genetic analysis by Sanger sequencing of the HBA genes identified a pathogenic variant, HBA2:c.262C>T, corresponding to the already described Hb M-Iwate [alpha2 87(F8) His>Tyr] in the propositus and in his similarly affected mother (Figure 1A). This Hb variant could be detected by high-performance liquid chromatography (HPLC) (Beta-Thalassemia Program, Bio-Rad) (Figures 1B and 1C).

The M Hbs are transmitted in an autosomal dominant fashion and the existence of familial cyanosis with this pattern of inheritance was first recognized in Japan more than 200 years ago. In the 1950s, Shibata et al. [7] discovered the cyanosis to be due to an abnormal Hb in a large family with about 70 affected individuals. This abnormal Hb was later given the name Hb M-Iwate. In the vivid description of the clinical picture by Shibata et al. [8], “The patients with this disease are cyanotic from childhood, looking like a man who has been swimming in a cold water pool for a long time”.

In conclusion, M Hbs should be considered in the differential diagnosis of cyanosis in the newborn period. HPLC can identify the presence of an Hb variant but gene sequencing is necessary for the identification of abnormal variants. Except for cosmetic consequences, the clinical course of patients with Hb M-Iwate is unremarkable.

### Table 1. Complete blood count parameters of the proband and his mother on the first postnatal day.

|       | Proband | Mother |
|-------|---------|--------|
| Hb (g/dL) | 19.1 | 11.2 |
| Hct (%) | 50.2 | 32.3 |
| RBC (10^6/µL) | 5.06 | 3.74 |
| MCV (fl) | 99 | 87 |
| MCH (pg) | 37.7 | 29.9 |
| MCHC (g/dL) | 38.0 | 34.2 |
| RDW (%) | 13.8 | 10.6 |
| WBC (10^3/µL) | 23.2 | 9.0 |
| Plt (10^3/µL) | 246 | 258 |

Hb: Hemoglobin, Hct: hematocrit, RBC: red blood cell count, MCV: mean corpuscular volume, MCH: mean corpuscular Hb, MCHC: mean corpuscular Hb concentration, RDW: red cell distribution width, WBC: white blood cell count, Plt: platelet count.
To the Editor,

We read the report by Büyükşimşek et al., [1] “Atypical Radiologic Image Characterized by Cavitary Lung Lesions in a Case of Hodgkin Lymphoma” (HL), with great interest. Büyükşimşek et al. [1] reported on a case of HL presenting with abnormal lung radiologic imaging and mentioned that “Disseminated cavitary lesions mimicking tuberculosis or other opportunistic infections in a case of HL is interesting and differential diagnosis is very important”. We would like to share our ideas regarding this observation. Indeed, lung involvement due to lymphoma is possible. Nevertheless, the concurrence between HL and tuberculosis is detectable. In endemic areas of tuberculosis, such as Southeast Asia, tuberculosis screening is routinely done for any cancerous patients, including those with HL. Pathophysiologically, a common pathway that can result in increased risk for tuberculosis among patients with HL is the alteration of the antioxidative system. The depletion of glutathione (GSH) due to HL [2] can increase the risk for tuberculosis since GSH plays an important role in defending against mycobacterial pathogens [3]. Considering the present report by Büyükşimşek et al., [1] there is an interesting question of whether the present case of HL had a concurrent tuberculosis infection or not. Büyükşimşek et al. [1] used the QuantiFERON test for exclusion of tuberculosis. In a recent report, the sensitivity and specificity of the QuantiFERON test were found to be poor [4]. In cases with underlying vitamin B12 deficiency, false negative results by QuantiFERON are possible [5]. In a recent report, vitamin B12 deficiency was observable in 0.54% of patients with HL and anemia [6].

Keywords: Hodgkin Lymphoma, Tuberculosis, Radiology

Conflict of Interest: The authors of this paper have no conflicts of interest including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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