The Hypoxia-Induced Acute Chest Syndrome of Transgenic Sickle Mice: Comparison between the Micro MR Images and Histo-pathological Findings

H. Uematsu[1], M. Takahashi[2], T. Asakura[3], I. Hasegawa[2], H. Hatabu[2]

[1]Department of Radiology, University of Fukui, Fukui-city, Fukui, Japan, [2]Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [3]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Abstract

Acute chest syndrome (ACS), a syndrome caused by the occlusion of pulmonary blood vessels by rigid sickled cells, is a leading cause of morbidity and mortality in patients with sickle cell disease. The aim of this study was to substantiate the usefulness of the magnetic resonance (MR) imaging as a diagnostic tool for ACS in transgenic (Tg) sickle mice that produce human sickle hemoglobin. Four Tg sickle mice were included in the present study, and 1 wild-type mouse was also evaluated as a reference. Upon exposure of these Tg sickle mice to hypoxia (5% oxygen), they died from sickling-dependent pulmonary sequestration. The lobes of the unilateral lung of the Tg sickle mice that died were removed and subjected to micro MR imaging (9.4 Tesla) using a voxel size of 19.5 x 19.5 x 500 µm. The micro MR images showed inhomogeneous diffuse areas due to increased signal intensity along with the enlarged blood vessels in the lungs, while such MR findings were not observed in the lung of the wild-type mouse that was also exposed to hypoxia. The changes in the micro MR images showed good agreement with gross pathologic findings in all cases. Micro MR imaging may be useful for early diagnosis of acute chest syndrome in sickle cell disease.

Objective

Sickle cell disease is a genetic blood disorder caused by a point mutation that results in a valine-to-glutamic acid substitution at the 6th position of the β-globin chains of hemoglobin (Hb). Under hypoxic conditions, the deoxygenated sickle Hb polymerizes, causing sickling of red blood cells. Acute chest syndrome (ACS) is a leading cause of morbidity and mortality in patients with sickle cell disease. Although the molecular and cellular basis of ACS has been elucidated, the early diagnosis/early treatment of ACS has not been established. High-resolution computed tomography (CT) provides insight into lung pathology based on x-ray attenuation between bone, soft tissue and air. However, the spatial resolution of CT technology is potentially limited by the gantry size, collimation, radiation dose, and scattering of radiation. Magnetic resonance (MR) microscopy provides both high spatial resolution and a large signal-to-noise ratio, which are necessary to depict small objects (1). We hypothesized that micro MR imaging would be able to detect changes in the lungs of transgenic (Tg) sickle mice with hypoxia-induced ACS. Our aim was to substantiate the usefulness of the MR imaging method as a diagnostic tool for ACS in Tg sickle mice.

Materials and Methods

Tg sickle mice (N=4) that produce 100% human β^s-globin (2) were selected for this study, because these mice are relatively healthy under normoxic condition but nearly exclusively develop sickling-dependent pulmonary sequestration upon exposure to hypoxia. One wild-type mouse was also evaluated as a reference. In order to determine the percentage of sickled cells, venous blood samples were collected every 5-10 min without exposure to air (3) before and during hypoxia exposure (5% oxygen). After death due to pulmonary sequestration, the lungs were inflated by tracheotomy to 14 cm H_2O pressure with air. The lobes of the unilateral lung were removed and subjected to MR imaging. MR images were obtained on a 9.4 Tesla DMX-400 MR machine (Bruker Instruments, Karlsruhe, Germany) using a 10-mm-i.d. birdcage coil. Spin-Echo imaging (TR/TE: 4000/3.4 ms, NEX: 4, FOV: 10 mm x 10 mm, matrix size: 512 x 512, slice thickness: 500 µm) was also used (voxel sizes of 19.5 x 19.5 x 500 µm). The lungs of MR images of Tg sickle mice were compared with gross pathologic specimens (hematoxylin-eosin (HE) staining) and rated on a three-point scale as follows: when the changes in the MR image matches the pathologic changes (Score 3), when the changes in the MR image roughly matches the pathologic changes (Score 2), and when the changes in the MR image does not match the pathologic changes (Score 1).

Results

In all 4 mice, the percentage of sickled cells in the venous blood increased upon exposure to hypoxia (Fig. 1). In all cases, the capillaries and small blood vessels of the lungs were occluded by massive numbers of deformed red blood cells (Fig. 2). MR imaging of the lungs showed inflation of the pulmonary arteries and the increase in the signal intensities along the vasculature (Fig. 2). No such findings were observed in the lungs of wild-type mouse (Fig. 3). The spatial distribution of the pathological processes identified by MR imaging showed good agreement with the gross pathologic changes in all cases (Score 3).

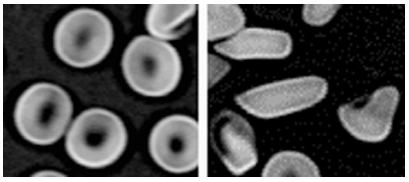

Figure 1. Pictures of erythrocytes in the blood of Tg sickle mice before (left) and 10 minutes after (right) exposure to hypoxia (5% oxygen).

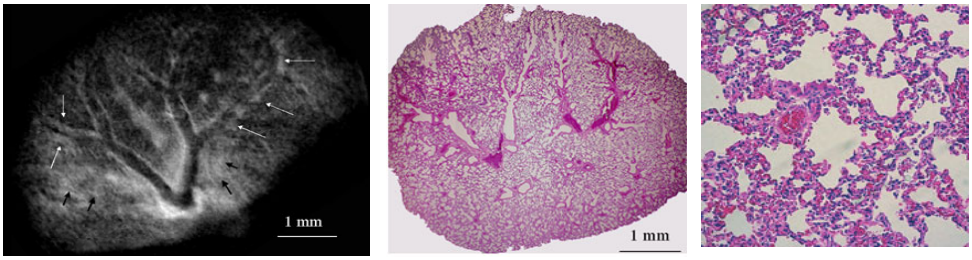

Figure 2. Left: Micro MR image of the lung with acute chest syndrome. Note that inflation of the pulmonary arteries (white arrows) with increased signal intensities along the vasculature (black arrows). Middle: Histological view of the same lungs (HE staining, x 20). Right: Histology of the section of the lungs (HE staining, x 200).

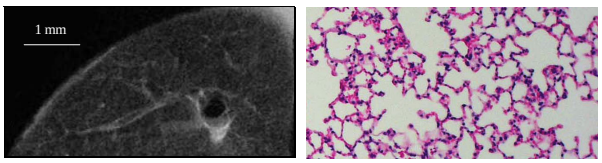

Figure 3. Left: Micro MR image of the lung of wild-type mouse after hypoxic exposure. Right: Histology of the section of the lung (HE staining, x200).

References

1. Johnson GA, et al. Radiology 2002; 222: 789
2. Reilly MP, et al. Exp Hematol 1994; 22: 501
3. Asakura T, et al. Proc. Natl. Acd. Sci.1994; 91:12589

Discussion

To the best of our knowledge, this is the first report which describes the correlation between the ultra high-resolution micro MR images and pathologic changes in the lung of Tg sickle mice that died from hypoxia-induced pulmonary sequestration or ACD. MR images clearly depicted the inflation of the pulmonary arteries associated with increase in the signal intensities along the vasculature. None of these changes were observed in the lungs of hypoxia-exposed wild-type mouse. Micro MR imaging may be able to detect the sickling-dependent vascular embolism of pulmonary vessels. This method may be used for the diagnosis of sickling-dependent pulmonary vaso-occlusion or ACD in patients with sickle cell disease.