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Heterogeneity of intrahepatic iron deposition in transfusion-dependent iron overload patients with hematological malignancies

Chronic red blood cell transfusion has been reported to induce secondary iron overload, which may result in hepatic, cardiac, and endocrine dysfunctions due to the production of reactive oxygen species (ROS) [1]. Survival from transfusion-related iron overload syndrome has markedly improved in the last decade because of the launch of deferasirox. It is now regarded as a first-line iron chelation therapy (ICT) for bone marrow failure syndrome or hematological malignancies patients with transfusion-dependent iron overload [2,3]. The optimal timing to start ICT remains unclear because a method to precisely monitor body iron stores has not yet been established. Serum ferritin (SF) is currently the most convenient and commonly used metric to monitor body iron stores despite the improved availability of advanced imaging techniques. Therefore, guidelines in various countries adopt SF levels as one of the references to start ICT [1,4,5].

However, there are some issues to be resolved. First, the relationship between body iron stores and SF levels is affected by many factors such as inflammation, infection, liver diseases which are common complications in patients with hematological malignancies [6,7]. Liver iron concentrations (LIC) are regarded as an indicator of the total body iron store, and the measurement of R2 and R2* values by magnetic resonance imaging (MRI) is a standard imaging technique for evaluating LIC [8,9]. Based on a previously reported protocol, FerriScan (Resonance Health & Resonance Health Analysis Services, Claremont, Australia) has been established and is a commercially available method to quantify LIC accurately and effectively [10,11]. This technique is not used in every institution due to limitations such as its high cost and the need for special software. The application of computed tomography (CT), which is easy to use and widely applied to measure LIC, needs to be considered. However, conventional single energy CT (SECT) has limitations for the detection of LIC due to normal variations in CT attenuation, predominantly in patients with mild iron overload. Moreover, SECT fails to detect iron in fatty livers, which has an inverse effect on attenuation by lowering CT numbers [12].

Second, iron distribution was previously reported to be heterogeneous in chemical and histochemical studies on LIC using biopsy and autopsy specimens [13–15]. This heterogeneity is not recognized by imaging techniques including MRI, and, thus, a clearer understanding of it may contribute to more accurate evaluations of body iron stores and the initiation of optimal ICT.

Dual-energy CT (DECT) is a recently developed new technique that provides additional information over that by SECT on tissue compositions. This technique is based on substances showing different densities with two different energies, with each substance displaying its own energy-dependent change in CT attenuation [16]. Therefore, DECT may represent a useful tool for the non-invasive quantification of the content of iron in the liver or other organs. In recent phantom and animal experiments, co-existing hepatic iron and fat were separated and LIC was accurately quantified by DECT [17–19]. The hepatic virtual iron content (VIC) measured by DECT was shown to correlate with MRI-measured LIC [20,21]. We herein analyzed intrahepatic iron distribution in transfusion-related iron overload patients with hematological malignancies or bone marrow failure syndrome by DECT.

Fourteen blood transfusion-dependent patients with hematological malignancies or bone marrow failure syndrome underwent liver DECT, and their SF levels were measured at Niigata University Medical and Dental Hospital. SF levels were measured using a chemiluminescent enzyme immunoassay. All patients provided informed consent in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of Niigata University Medical and Dental Hospital. The characteristics of these patients are shown in Table 1. The median time between DECT and the SF level examination was 1.5 days (range, 0–25). Two patients received ICT, and both patients were administered deferasirox.

CT was performed using a dual source 128-slice CT system (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) equipped with an additional tin filter (Sn) for improved separation of the two energy spectra [22]. DECT scanning was performed using a tube voltage pair of Sn 140 kV and 80 kV or Sn 140 kV and 100 kV. DECT images were acquired using the three-material decomposition algorithm of fat, soft tissue, and iron, and iron deposition was visualized as a red signal.

Representative DECT images of the liver are shown in Fig. 1. We classified DECT images into three groups: no (a), focal (b–d), and diffuse deposition (e–h). Among the 14 patients, 1 had no, 4 had focal, and 9 had diffuse iron deposition. In the 4 patients with focal iron deposition, iron was deposited in the left lobe of the liver only. In Fig. 1b–d, iron deposition appeared to spread gradually from the left lobe to the

Table 1
Patient's characteristics.

Patient No.	Age (y)	Sex	Diagnosis	SCT	ICT	Blood transfusion (units)*	SF level (ng/ml)
1	54	M	MDS (RARS)	No	No	N/A	961
2.	37	M	AML	Yes	No	54	6113
3	66	F	AML	Yes	No	N/A	2168
4	57	M	MDS (RCMD)	No	Yes	148	4042
5	65	M	AML	No	Yes	82	795
6	47	M	AML	Yes	No	N/A	1921
7	52	F	AA	No	No	92	5104
8	56	F	AML	No	No	36	2916
9	37	M	ALL	Yes	No	N/A	2346
10	48	F	AML	Yes	No	150	2519
11	25	M	AML	Yes	No	46	1645
12	53	F	MDS (RAEB-2)	No	No	66	1240
13	43	F	AML	Yes	No	78	3765
14	68	M	AA	No	No	30	5803

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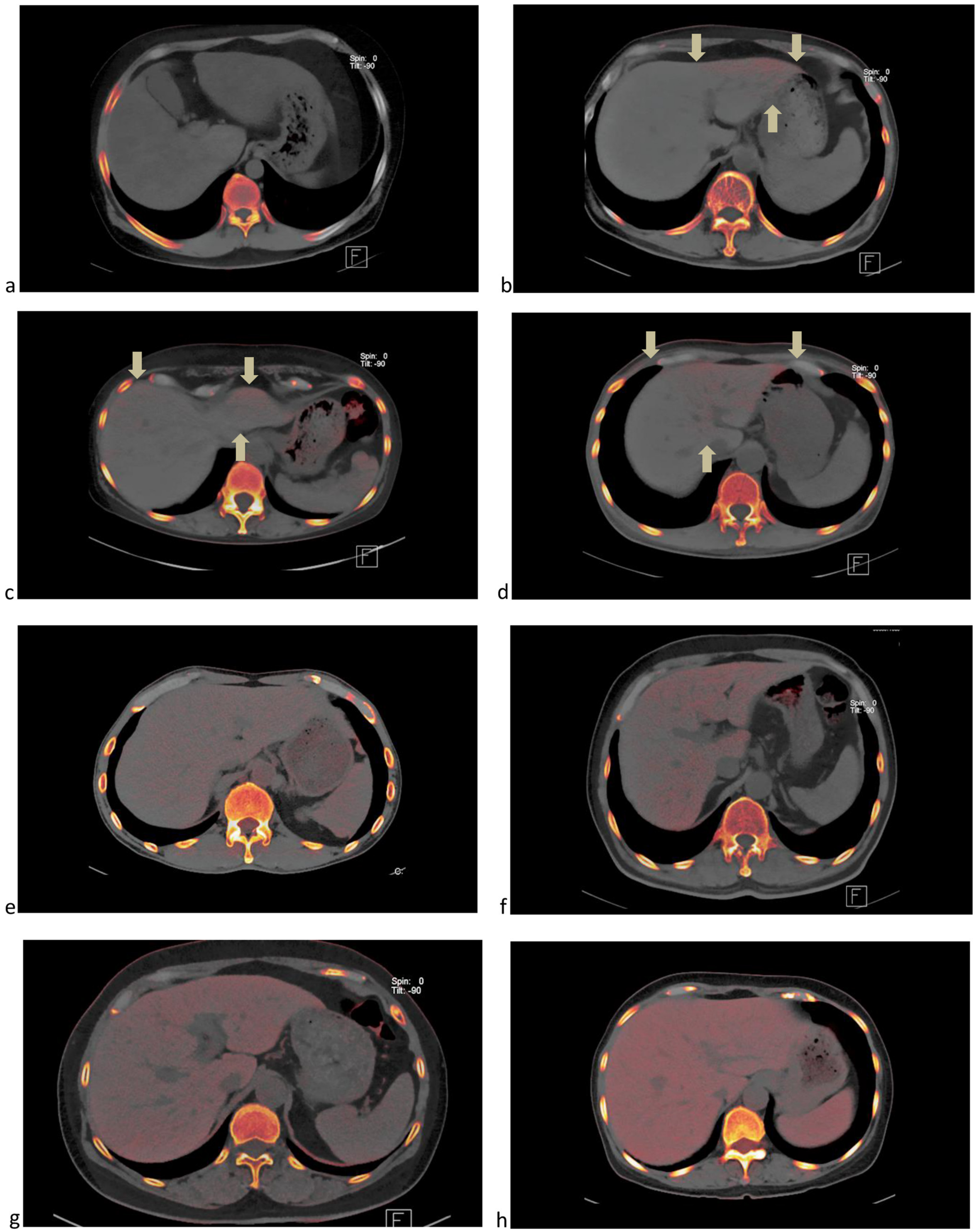

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right lobe. Of note, among patients who showed diffuse iron deposition, the extent of its deposition differed for each case. To the best of our knowledge, this is the first study to show the heterogeneity of the hepatic lobar distribution of iron in transfusion-dependent patients using this imaging technique. Our results indicated that DECT is useful for analyses on the heterogeneity of intrahepatic iron distribution.