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Evaluating and monitoring bone marrow hypoplasia in adults with aplastic anemia via high-resolution iliac magnetic resonance imaging in the current era

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Abstract

The diagnosis and monitoring of aplastic anemia (AA) rely heavily on a complete blood count (CBC), and multiple-site bone marrow (BM) aspirations and biopsies. However, these approaches have certain limitations. We aimed to assess high-resolution magnetic resonance imaging (MRI) as a complementary approach for evaluating BM hypoplasia and monitoring treatment response in adults with AA in the current era.

Twelve newly diagnosed AA patients and 12 sex- and age-matched healthy controls were enrolled in this study from January 2017 to August 2018. A bilateral iliac 3.0T MRI was used to collect data for each subject, and the signal intensity on the T1-weighted images (T1WIs) were expressed as a contrast-to-noise ratio (CNR). The MRI, CBC, and BM biopsy data were analyzed and compared.

A qualitative analysis identified a significant difference in MRI signal characteristics between the AA group and the healthy control group. The clinical classifications of very severe aplastic anemia (VSAA) and severe aplastic anemia (SAA) corresponded to pattern I and pattern II on the MR images, respectively. However, this imaging classification did not correlate with the biopsy-based BM cellularity measure. A quantitative analysis showed a significantly higher signal intensity in AA patients than in controls. A within-group comparison revealed that more severe types of AA, based on the clinical classification, corresponded to stronger signals. Notably, MRI could detect treatment response earlier than CBC, regardless of whether there were improvements in hematopoiesis.

MRI can be used to predict the therapeutic effects in patients with AA and is an important complementary tool for evaluating and monitoring BM hypoplasia.

Abbreviations: AA = aplastic anemia, ANC = absolute neutrophil count, BM = bone marrow, CBC = complete blood count, CNR = contrast-to-noise ratio, Hb = hemoglobin, MRI = magnetic resonance imaging, NSAA = non-severe aplastic anemia, PLT = platelet count, RBC = red blood cell count, ROI = region of interest, SAA = severe aplastic anemia, T1WI = T1-weighted image, T2WI-FS = fat-suppressed T2-weighted image, VSAA = very severe aplastic anemia, WBC = white blood cell count.

Keywords: bone marrow, hematopoiesis, magnetic resonance imaging, therapeutic effects

1. Introduction

Aplastic anemia (AA), a disease that leads to bone marrow (BM) failure, is characterized by pancytopenia and BM hypoplasia.[1–4] Histologically, the hallmark of AA is damage to hematopoietic stem cells and their replacement by adipose tissue.[5,6] In clinical practice, the diagnosis and monitoring of AA rely heavily on a complete blood count (CBC), and multiple-site BM aspirations and biopsies.[7–9] BM examinations are invasive, and the findings from different puncture sites can vary significantly due to the uneven distribution of hematopoietic tissues. CBC is often used to

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evaluate and monitor treatment response, but there is a clear time lag between BM status and its blood manifestations. Consequently, there is a need for noninvasive approaches that can help visualize the current BM status within a sufficiently large area and capture early changes in the BM.

Previous studies demonstrated that AA patients have unique BM characteristics on 1.5T or lower field strength magnetic resonance imaging (MRI).[10–14] However, all of these studies presented a very limited number of cases, and the potential value of MRI for AA assessment was not fully explored. High-resolution MRI is capable of visualizing highly detailed anatomical structures of the BM and enables the detection of BM dynamics with great accuracy.[15] Compared to the previous studies, a comparatively larger number of patients with AA were examined via 3.0T MRI scans in the present study. The value of MRI in evaluating BM hypoplasia and monitoring treatment response in AA was investigated.

2. Materials and methods

2.1. Subjects

The research protocol was approved by the Ethics Committee of Zhengzhou University People's Hospital, and each participant signed an informed consent form before enrollment. Twelve newly diagnosed AA patients admitted to the Zhengzhou University People's Hospital from January 2017 to August 2018 were enrolled in this study, and another 12 sex- and age-matched healthy persons were selected to serve as controls. Each group was composed of 10 male and 2 female subjects, with a mean age of 34 (25–61) years.

In the AA group, there were 2 cases of very severe aplastic anemia (VSAA), 4 cases of severe aplastic anemia (SAA), and 6 cases of non-severe aplastic anemia (NSAA). The whole patients underwent CBC, BM biopsy and bilateral iliac MRI within three days of admission, respectively. And MRI of the corresponding sites was performed in the healthy control group for comparison without BM biopsy. The guidelines proposed by Killick et al. (Adult British Society for Hematology AA Guidelines)[7] for the diagnosis and management of adult AA were used in our study. To investigate the clinical value of MRI scans in monitoring the therapeutic effects of patients with AA, we selected 6 patients, including 3 treatment-responsive and 3 treatment-unresponsive patients, to conduct a post-treatment follow-up and comparison of the MRI and CBC data at different time points.

2.2. Magnetic resonance imaging

MRI of the BM was performed with a 3.0T (GE Medical Systems Discovery MR750, WI) superconductive MR unit. Horizontal T1-weighted images (T1WIs, repetition time (TR)/ echo time (TE) = 570/6.5 ms) and fat-suppressed T2-weighted images (T2WIs-FS, TR/ TE = 2500/65 ms) of the bilateral iliac bones were obtained. Imaging was conducted with 6-mm slice thickness, a 1-mm intersection gap and a matrix size of 320 × 224.

The MR images were reviewed by 2 radiologists, and the interpretations were considered valid when both radiologists were in agreement. In the qualitative analysis, the relatively fixed muscle signal was used as the reference. The obtained MRI signals were classified as equal, high or low. The imaging features of the BM from the bilateral iliac bones on both T1WIs and T2WIs-FS were judged visually, and three distinct patterns were established according to the signal distribution in AA patients. Pattern I was characterized by uniform and diffusely distributed high signals on T1WIs and low signals on T2WIs-FS. Pattern II was defined by the localized distribution of dotted low signal foci on T1WIs, which was observable on a high signal background, and a few dotted high signal foci on T2WIs-FS on a low signal background. Pattern III was characterized by a diffusely distributed mixture of high and low signals on T1WIs and T2WIs-FS. The imaging features of the three patterns on T1WIs in AA patients are shown in Figure 1.

In the quantitative analysis, the broadest visible plane of the bilateral iliac bones in the transverse section was selected as the region of interest (ROI). The signal intensity (S) and standard

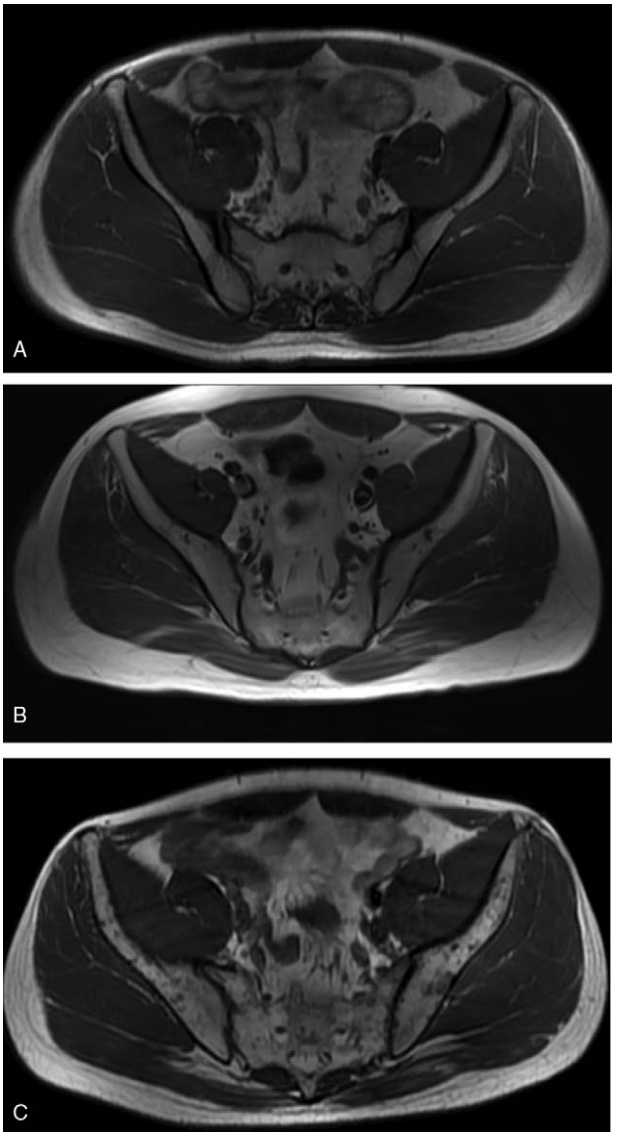

Figure 1. Three MRI distribution patterns on T1WIs in AA patients. (A) The T1WI showed uniform and diffusely distributed high signals (Pattern I); (B) The T1WI exhibited the localized distribution of dotted low signal foci in a high signal background (Pattern II); (C) The T1WI revealed a diffusely distributed mixture of high and low signals (Pattern III). AA = aplastic anemia, MRI = magnetic resonance imaging, T1WI = T1-weighted image.

deviation (σ) of the iliac bones and surrounding muscles were measured. Signal intensity was expressed quantitatively as a contrast-to-noise ratio (CNR) = |S1-S2|/ $(\sigma 1 - \sigma 2)^{1/2}$. Thus, the signal intensities of the left and right iliac bones were denoted by CNR_{left} and CNR_{right}, respectively. The signal intensity of the bilateral iliac bones was labeled as $CNR_{left+right}$.

2.3. Statistical analysis

Signal intensity was expressed as the mean ± standard deviation (x ± s). An independent sample *t* test was used to compare the signal intensities between the 2 groups as described in the figure legends. The difference in signal intensity between the left and right iliac bones of the same person was analyzed by a paired sample *t* test. Pearson correlation analysis was used to examine the relationship between signal intensity and age in the healthy controls. In all tests, a *P* value less than .05 was considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL) for Windows.

3. Results

3.1. MRI findings in the healthy control group

In healthy controls, there were consistent signals with slightly high intensity on T1WI and slightly low intensity on T2WI-FS, which were interpreted as signs of active proliferation (Fig. 2).

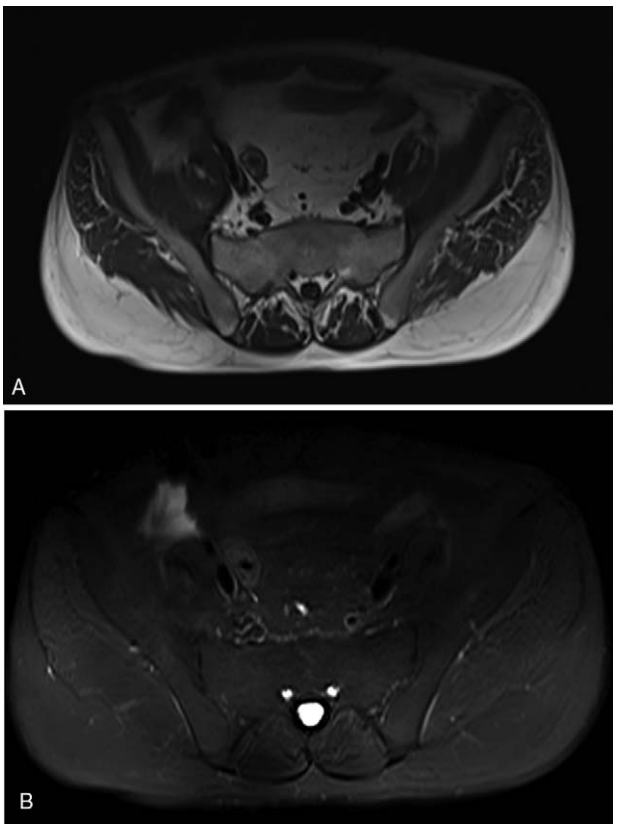

Figure 2. The MRI characteristics of the healthy control group. (A) MRI scans demonstrated the slightly high signal intensity on T1WI and (B) slightly low intensity on T2WI-FS in the healthy control group. MRI = magnetic resonance imaging, T1WI = T1-weighted image, T2WI-FS = fat-suppressed T2-weighted image.

Table 1

Comparison of the signal intensities between the left and right iliac bones in the healthy control and AA groups.

Groups	Cases	CNR_{left}	CNR_{right}	*P* value
Healthy Control group	12	27.73 ± 6.13	27.53 ± 8.00	.89
AA group	12	46.42 ± 11.34	50.68 ± 10.04	.20

The CNR_{left} was 27.73 ± 6.13, the CNR_{right} was 27.53 ± 8.00, and the $CNR_{left+right}$ was 55.26 ± 13.37.

The MR images of the bilateral iliac bones were largely uniform (Fig. 2), and there was no significant difference in signal intensity between the left and right iliac bones on T1WIs ($P = .89$) (Table 1). Considering that the MRI of the BM varies with age, the correlation between signal intensity and age in the healthy controls was analyzed. The Pearson correlation analysis revealed that the $CNR_{left+right}$ was significantly correlated with age at the 0.01 level (r = .78, $P = .003$) (Fig. 3).

3.2. MRI findings in the AA group

The AA group showed markedly high signals on T1WIs and mixed low signals on T2WIs-FS with considerable heterogeneity, which were believed to be signs of myeloid hypoplasia (Fig. 4). The CNR_{left} was 46.42 ± 11.34, the CNR_{right} was 50.68 ± 10.04, and the $CNR_{left+right}$ was 97.11 ± 18.42.

Unlike in the healthy controls, the AA patients showed an apparent difference between the matching areas of the BM in the left and right iliac bones in the comparative MRI analysis (Fig. 4). However, the quantitative analysis did not detect a significant difference in signal intensity on T1WIs ($P = .20$) (Table 1).

3.3. Comparison of MRI results between the AA group and the healthy control group

The MRI scans in the AA group showed an increase in high signal areas on T1WIs and low signal areas on T2WIs-FS compare to those in the healthy group. The $CNR_{left+right}$ in the AA group was significantly higher than that in the control group (97.11 ± 18.42 vs 55.26 ± 13.37, $P < .001$) (Fig. 5).

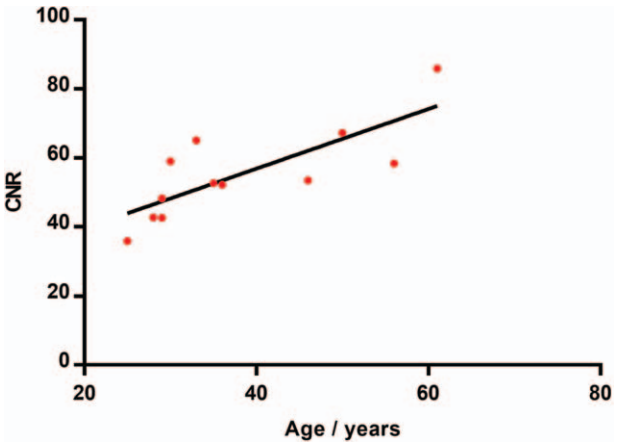

Figure 3. A scatter plot depicting age (years) on the X axis plotted against CNR on the Y axis in the healthy controls; the regression line is shown as a black line (r = 0.78, $P = .003$). CNR = contrast-to-noise ratio.

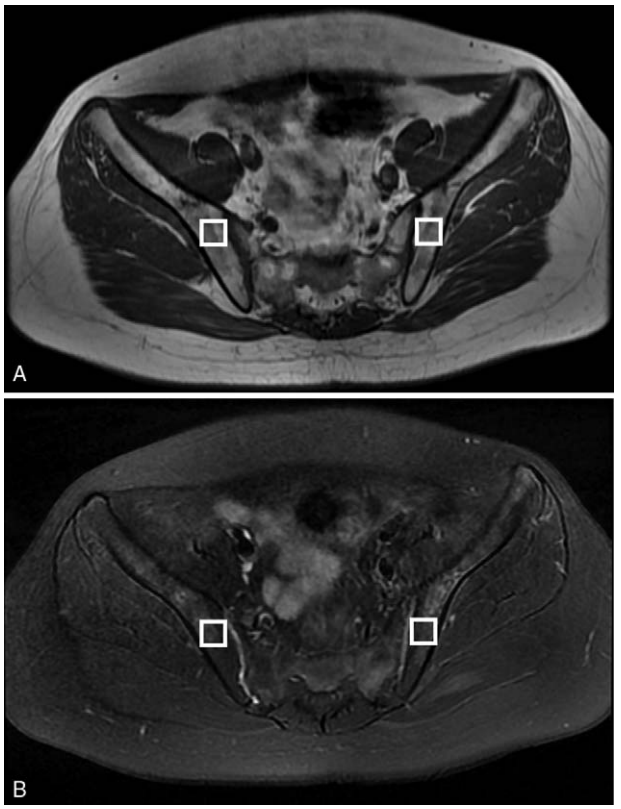

Figure 4. The MRI characteristics of the AA group. (A) MRI scans illustrated markedly high signals on T1WI and (B) mixed low signals on T2WI-FS in the AA group. The white squares indicated an apparent difference of imaging distribution between the matching areas in the left and right iliac bones. AA = aplastic anemia, MRI = magnetic resonance imaging, T1WI = T1-weighted image, T2WI-FS = fat-suppressed T2-weighted image.

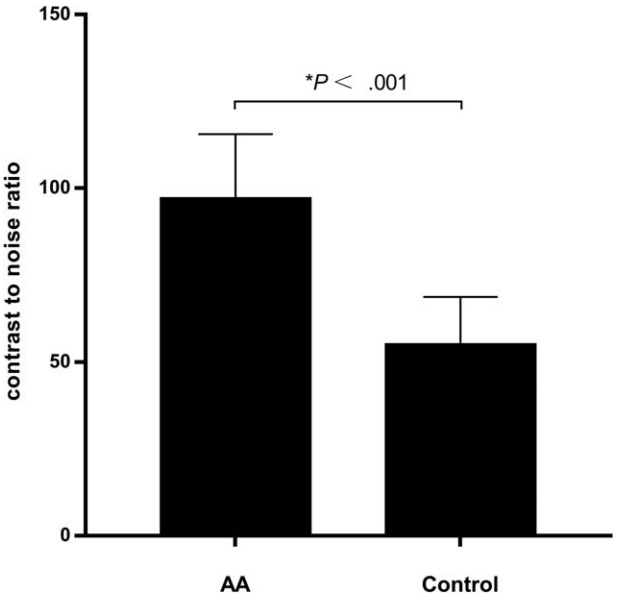

Figure 5. Comparison of the signal intensity between the AA group and the healthy control group. AA = aplastic anemia.

3.4. Correlation between MRI results and AA severity

The qualitative analysis showed that the both cases with pattern I were classified as VSAA. The scans with pattern II were composed of 4 SAA cases and 1 NSAA case, and the cases with pattern III were all classified as NSAA (Table 2). In the quantitative analysis, the within-group comparison revealed a significant difference in signal intensity between different levels of disease severity (SAA/VSAA: 109.40 ± 9.12, NSAA: 84.82 ± 17.33, $P = .01$) (Fig. 6). A more severe level corresponded to a stronger signal.

3.5. Correlation between MRI and biopsy results

Pattern I on the MR images corresponded to an extreme reduction in BM hypoplasia in the biopsy. However, the BM biopsy results of cases with pattern II and III exhibited different degrees of BM hypoplasia, including extreme reductions, significant reductions and reductions (Table 2).

Table 2

Summary of the clinical and imaging characteristics of the 12 patients newly diagnosed with AA.

		Complete Blood Count					Biopsy result			MRI	
Patients	Age/ Sex	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	RBC ($\times 10^{12}$/L)	Hb (g/L)	PLT ($\times 10^9$/L)	Megakaryocytes	Degree of proliferation	Hematopoietic cell surface area	Imaging classification	Clinical Classification
1	28/M	1.49	0.05	2.50	76	11	none	Extremely reduced	<20%	I	VSAA
2	33/M	1.17	0.14	1.90	58	14	none	Extremely reduced	<20%	I	VSAA
3	35/M	3.46	0.86	1.97	71	24	none	Extremely reduced	<20%	II	SAA
4	50/M	3.14	0.56	1.87	65	7	none	Significantly reduced	20%	II	SAA
5	61/F	1.70	0.44	2.14	69	13	none	Significantly reduced	20%–30%	II	SAA
6	29/M	1.49	0.86	1.70	55	6	none	Reduced	30%–40%	II	SAA
7	46/M	3.12	1.35	3.47	116	41	none	–*	–*	II	NSAA
8	36/F	2.88	1.27	2.79	102	23	none	Extremely reduced	<20%	III	NSAA
9	25/M	3.26	0.80	2.38	61	33	rare	Significantly reduced	20%–30%	III	NSAA
10	29/M	3.55	1.40	2.81	98	33	none	Reduced	<40%	III	NSAA
11	56/M	3.25	1.97	3.22	114	32	none	Reduced	30%–40%	III	NSAA
12	30/M	1.55	0.78	1.99	72	23	rare	–†	–†	III	NSAA

They all showed a small number of granulocytes and rare or no megakaryocytes. Thus, the degrees of proliferation were not assessed.

AA = aplastic anemia, ANC = absolute neutrophil count, F = female, Hb = hemoglobin, M = male, NSAA = non-severe aplastic anemia, PLT = platelet count, RBC = red blood cell count, SAA = severe aplastic anemia, VSAA = very severe aplastic anemia, WBC = white blood cell count.

* there existed more cortical bone tissues in the bone marrow biopsy sample.

† there were areas of hemorrhage in the bone marrow biopsy sample.

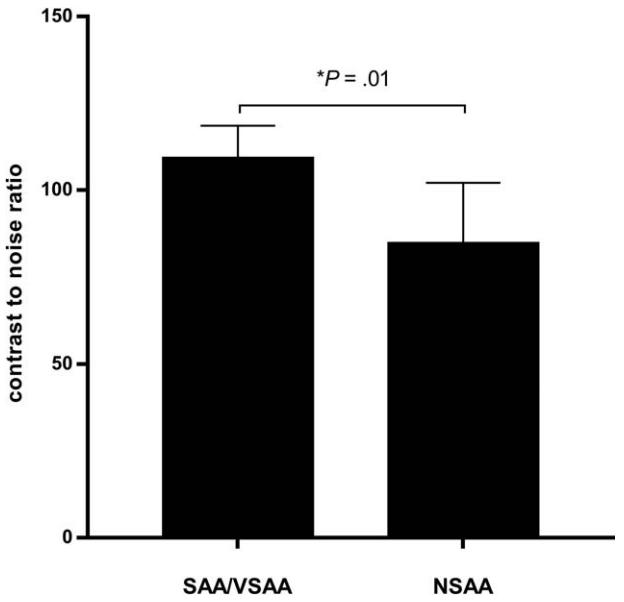

Figure 6. Comparison of the signal intensity between the SAA/VSAA cases and the NSAA cases. NSAA = non-severe aplastic anemia, SAA = severe aplastic anemia, VSAA = very severe aplastic anemia.

3.6. MRI to monitor bone marrow hematopoiesis in AA patients

Six AA patients were selected for a long-term follow-up via MRI and CBC. Three treatment-responsive patients showed improvements in hematopoiesis detected by MRI, which were consistent with the CBC data obtained 1 month later. Similarly, 3 treatment-unresponsive patients showed no improvements in hematopoiesis detected by MRI, which were later confirmed by CBC results (Table 3).

To clarify the significance of using MRI to monitor hematopoiesis in AA patients receiving treatment, we analyzed the MRI and CBC results of a treatment-responsive patient at different time points. As expected, the decreased CNR, which represented improved hematopoiesis, was correlated with increased absolute neutrophil count/hemoglobin/platelet count (ANC/Hb/PLT) (Fig. 7).

4. Discussion

AA is a T lymphocyte-mediated immune imbalance in which the hematopoietic system is actively targeted.[16–19] The red BM is gradually replaced by adipose tissue, thereby significantly altering the composition of the BM.[5,6,17,20] MRI, which is based on differences in the signal properties of fat, water molecules, proteins, and bone, can intuitively differentiate BM from adipose tissue to subsequently show the characteristic changes caused by lesions.[21–27]

Since MRI possesses the advantage of reflecting the current state of BM hematopoiesis, this imaging method has the potential to be used for evaluating and monitoring BM hypoplasia in adults with AA. In this study, we demonstrated via 3.0T MRI that there was a significant difference in signal characteristics between the AA group and the healthy control group, with the former manifesting qualitatively and quantitatively higher signals than the latter on T1WIs, as a result of increased fat content. Previous studies have also reported imaging characteristics of AA patients using 1.5T or lower field strength MRI in smaller samples than those used in our study. Discrepancies between those studies, especially in treatment response, were attributed to differences in patient age and the resolution of the MRI equipment.[10–14] The clinical application and significance of this approach have not been further studied in later research.

In our MRI comparative analysis, there was clearly a heterogeneous distribution of the BM in the left and right iliac bones of AA patients. However, the signal intensity of both sides on T1WIs did not show any significant difference in the quantitative analysis. The results suggest that MRI data, when analyzed quantitatively based on the largest visible plane of the iliac bones in the transverse section, may offer information about hematopoietic activity in AA patients that can be obtained only through multiple-site BM biopsy.

Notably, the MRI data were correlated with AA severity defined and classified by the CBC data. However, the MRI data did not correlate with biopsy-estimated BM cellularity measures, probably as a result of sampling inaccuracies inherent to BM biopsies due to the uneven distribution of hematopoietic tissues. Therefore, MRI could be a valuable noninvasive alternative to BM examinations to evaluate BM hypoplasia in adults with AA. More significantly, our study demonstrated that, regardless of whether there were improvements in hematopoiesis, MRI was able to detect treatment responses that would be detected by CBC

Table 3

The dynamic changes in CNR and ANC/Hb/PLT in 6 AA patients during treatment.

		CNR				ANC				Hb				PLT			
patients	Diagnosis	M_0	M_3	M_4	M_5	M_0	M_3	M_4	M_5	M_0	M_3	M_4	M_5	M_0	M_3	M_4	M_5
Treatment-responsive																	
1	SAA	**105.05**	**91.39**	89.16	68.52	**0.86**	0.67	**1.25**	1.80	**55**	63	**75**	101	**6**	3	**27**	46
2	NSAA	**82.42**	**71.02**	ND	ND	**0.80**	0.67	**1.58**	2.53	**61**	76	**90**	95	**33**	35	**52**	57
3	NSAA	**68.15**	69.07	**57.78**	ND	**0.78**	1.04	0.73	**2.12**	**72**	76	71	**80**	**23**	20	27	**44**
Treatment-unresponsive																	
4	VSAA	**120.11**	121.83	ND	ND	**0.05**	0.02	0.01	ND	**76**	69	66	ND	**11**	9	14	ND
5	NSAA	**71.65**	70.18	73.80	ND	**1.27**	1.02	0.95	1.19	**102**	101	96	98	**23**	26	24	26
6	NSAA	**108.18**	104.74	105.19	ND	**1.40**	1.03	0.93	1.09	**98**	91	99	99	**33**	45	33	29

M_0, M_3, M_4, and M_5 represented the time in initial diagnosis, 3 months, 4 months, and 5 months after treatment, respectively.

AA = aplastic anemia, ANC = absolute neutrophil count, $1 \times 10\text{^}9$/L, CNR = contrast-to-noise ratio, representing bilateral iliac signal intensity, Hb = hemoglobin, g/L, ND = not done, NSAA = non-severe aplastic anemia, PLT = platelet count, 1×10^9/L, SAA = severe aplastic anemia, VSAA = very severe aplastic anemia.

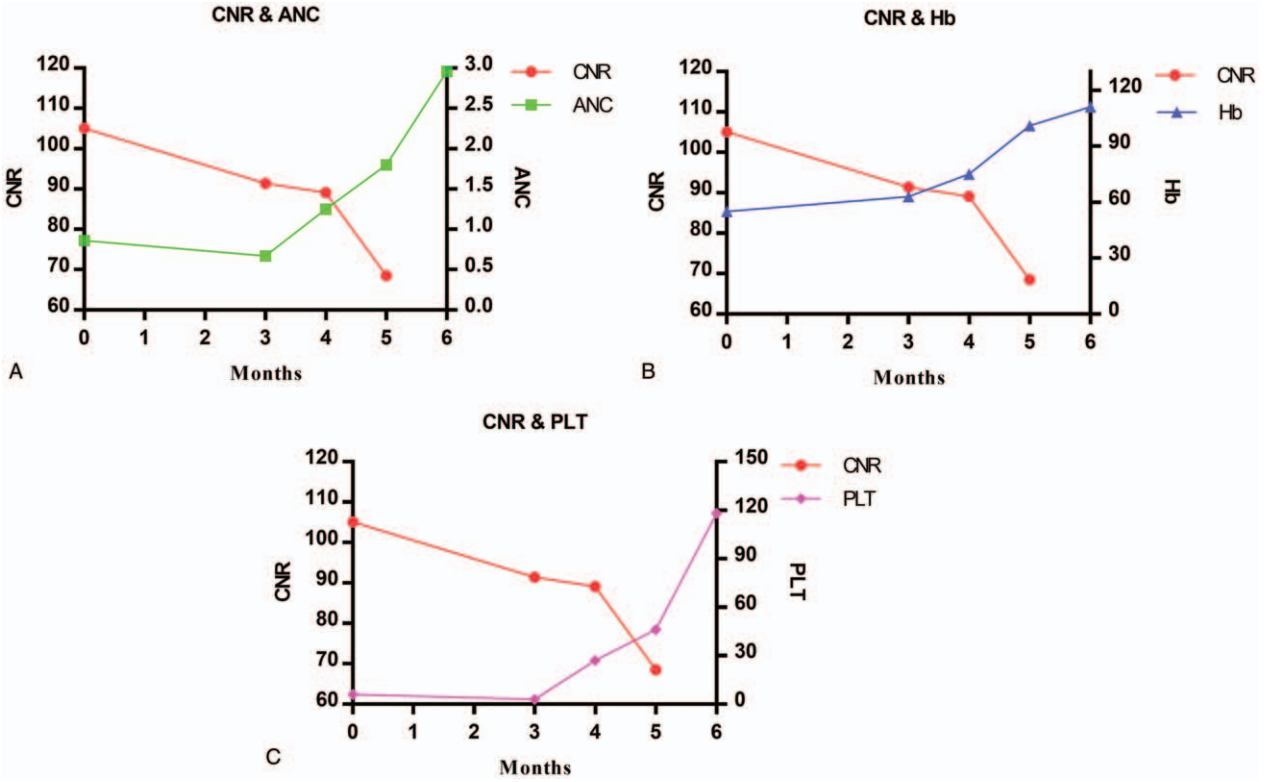

Figure 7. The follow-up results of a treatment-responsive patient demonstrated that the decreased CNR was correlated with increased ANC/Hb/PLT. ANC = absolute neutrophil count, CNR = contrast-to-noise ratio, Hb = hemoglobin, PLT = platelet count.

at a later time. Together with CBC, MRI may serve as an effective tool to assess the therapeutic effects in AA.

In our current study, we could not gain the adequate verification about the guiding role of iliac MRI in BM biopsy. Therefore, whether MRI evaluation prior to BM biopsy for aiding to detect the location of BM biopsy will be performed in future studies. With respect to the choice of bones for MRI scanning in AA patients, we focused our observation on the bilateral iliac bones, since these bones are the most common sites for BM examinations and are usually the first to be affected in the early stages of AA.[1] However, hematopoietic marrow also remains throughout life in the spine, sternum, ribs, skull, pelvis, calcaneus, and proximal metaphysis of the humerus and femur.[27,28] Thus, spine, sternum or even whole-body MRI needs to be investigated through larger scale studies in the future to identify the best location for MRI to monitor treatment response in AA patients.

5. Conclusion

MRI can be used to predict the therapeutic effects in patients with AA and represents an important complementary approach for evaluating and monitoring BM hypoplasia.

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