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CHEST RADIOLOGY

Cortical bone invasion in non-transfusion-dependent thalassemia: tumefactive extramedullary hematopoiesis reviewed

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Abstract
Objective of the study To assess the prevalence of cortical bone invasion (CBI) with secondary extramedullary hematopoiesis (EMH) in patients with non-transfusion-dependent thalassemia (NTDT), to determine its predilection sites on thoracic and abdominal imaging, to determine whether there is an association between various clinical and hematological parameters, and to evaluate its various findings mainly on magnetic resonance imaging (MRI), in addition to computed tomography (CT) scans.
Materials and methods This is a retrospective cohort study of 57 patients with NTDT imaged by CT or MRI. Both clinical and laboratory data were gathered. An imaging scoring system was used to describe the appearance of CBI by MRI.
Results Twenty-seven patients (47.4 %) were found to have CBI and EMH with the most common location being the thoracic spine. Splenectomy and lower hemoglobin level were found to be independent risk factors for its development. Most lesions were homogenous (70 %), had predominant red marrow signal (67 %), and well-defined margins (89 %).
Conclusion CBI and secondary tumefactive EMH are common findings in patients with NTDT, with distinct imaging and clinical characteristics. An increased risk was seen in patients with splenectomy and lower hemoglobin. The imaging scoring system described is helpful in diagnosing and describing this entity, hence precluding unnecessary biopsies.

Keywords Non-transfusion-dependent thalassemia · Extramedullary hematopoiesis · Cortical bone invasion · Soft tissue lesion

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Introduction

Non-transfusion-dependent thalassemias (NTDT) are part of a group of inherited hemoglobinopathies previously known to be endemic to certain areas of the world; however, lately they have been recognized as a growing global health concern [1]. Having milder clinical manifestations than transfusion-dependent thalassemias (TDT), NTDT patients do not require regular transfusion for survival [2]. However, they do suffer from complications due to ineffective erythropoiesis as well as hemolytic anemia, typically related to iron overload [3] and extramedullary hematopoiesis (EMH) [4].

Traditionally, EMH is defined as a non-neoplastic proliferation of hematopoietic tissue outside the bone marrow and peripheral blood [5]. This is used to describe extramedullary erythropoietic tissue (EMET) in the liver and spleen. Though initially microscopic, EMH can progress in size leading to a tumorlike mass involving any organ, a phenomenon called "Tumefactive EMH" [6]. These masses can be discovered incidentally or can grow large enough to cause significant symptoms.

Bone marrow expansion in thalassemia manifests as typical craniofacial changes [7]; however, deformities and thinning of the cortices of long bones and vertebrae, especially in the thoracic region, and to a lesser extent the lumbar region, also occur [4]. There can be secondary, cortical breaks or cortical bone invasion (CBI) by the expanded trabecular bone and by the formation of adjacent foci of erythropoietic tissue [8, 9], usually termed EMH in the literature. However, in our opinion, the term CBI better reflects the bone marrow expansion, cortical disruption, and subsequent formation of peri-/para-skeletal foci of erythropoiesis/hematopoiesis.

Hence, in our opinion, the concept of EMH should include two pathophysiologically different phenomena: CBI and EMET. Both are related to chronic hemolytic anemia and ineffective erythropoiesis; however, these two phenomena are different since one involves a systemic activation of hematopoietic cells outside the musculoskeletal system such as the spleen or liver, and the other involves overacting bone marrow and expansion of the intramedullary space into the soft tissues through a cortical break. The question as to whether there is an association between CBI and various clinical and hematological parameters in patients with NTDT has not been previously addressed.

The aims of this study were to assess the prevalence and characteristics of CBI in patients with NTDT, to determine the predilection sites of CBI on thoracic and abdominal imaging, to determine whether there is an association between various clinical and hematological parameters in these patients and to evaluate the various findings of CBI mainly on magnetic resonance imaging (MRI), as well as computed tomography (CT) imaging.

Materials and methods

Patients

This is a retrospective cohort study of all patients at the Chronic Care Center, which specializes in the treatment of patients with thalassemia, and who have been diagnosed with NTDT and imaged by MRI and/or CT scans for any reason. Institutional Review Board (IRB) approval has been obtained for this study.

Clinical data were gathered on NTDT patients from the medical records, including basic demographic information (age, sex, diagnosis), hemoglobin concentration at the time of imaging, platelet count, transfusion history, splenectomy status, fetal hemoglobin concentration, serum ferritin, and liver iron concentration. Transfusion history was classified as: regular (every 1–3 months), occasional (transfusion secondary to severe anemia due to infection, pregnancy, or surgery), and never transfused.

Radiological review

The imaging modalities were not uniform since this was a retrospective review of patients. The vast majority of images available were from MR examinations; therefore, this study relied mainly on MR features. The available CT scans of the chest and abdomen were performed for a variety of clinical indications using non-iodinated intravenous contrast material (Omnipaque, GE Healthcare, United Kingdom), using 64 MDCT scanner (Siemens Sensation, Germany) with bone window setting of 1.5 mm slice thickness. The MRIs were primarily obtained as part of another research study from our institution to assess liver iron load in thalassemic patients. These MR examinations were performed using axial T2-based spin-echo (SE) and fast field echo (FFE) sequences as follows: TR = 1000; TE = 6–18 (1.5 T Philips Ingenia, The Netherlands); or TR = 2500, TE = 6–18 (1.5 T Philips Intera, The Netherlands). There were three CT scans of the abdomen and pelvis, one CT scan of the chest, five chest MRIs, and 52 abdominal MRIs. The abdominal MR images were obtained from the mid-chest to the iliac crests. All imaging studies were reviewed by the senior author (NJK). The images were evaluated for the presence of CBI, which was defined as bone marrow expansion with cortical disruption and adjacent secondary soft tissue formation representing EMH.

A previously described scoring system was used based on MR imaging, which included five different variables: CBI score, fat score, homogeneity score, margins score, and bone marrow signal (BMS) score (Table 1) [10]. BMS and BM expansion were assessed in all patients regardless of their CBI score.

CBI score

A CBI score of 0 (no CBI) was assigned when there was no evidence of extramedullary soft tissue formation with no bone expansion. A score of 1 (probable CBI) was assigned when there was bone marrow expansion and adjacent secondary soft tissue formation, but no obvious disruption of the cortex (Figs. 1a, 2a, b, 3). A score of 2 (definite CBI) was assigned when there was definite cortical disruption along with bone marrow expansion and adjacent soft tissue formation (Figs. 1b, 2b, 3, 4, 5, 6). A score of 1 was upgraded to 2 when available CT scans showed evidence of cortical disruption (Fig. 2).

Fat score

A score of 0 was given when the juxtacortical soft tissue lesions showed only MR signals isointense to red marrow (Figs. 1a, 2a, b, 3). A score of 1 was given when signal

Table 1 Imaging scoring system

Variables	Score			
	0	1	2	3
CBI score	No EMH	EMH but no obvious cortical disruption on imaging	Obvious CBI on imaging	–
Fat score	No fat	Predominantly isointense to red marrow signal	Similar proportion of fatty and red marrow signal	Predominantly isointense to fatty marrow signal
Homogeneity score	–	Homogeneous	Heterogeneous	–
Margins score	–	Well defined	Not well defined	–
BMS score	–	Red	Fatty	–

EMH extramedullary hematopoiesis, *CBI* cortical bone invasion, *BMS* bone marrow signal

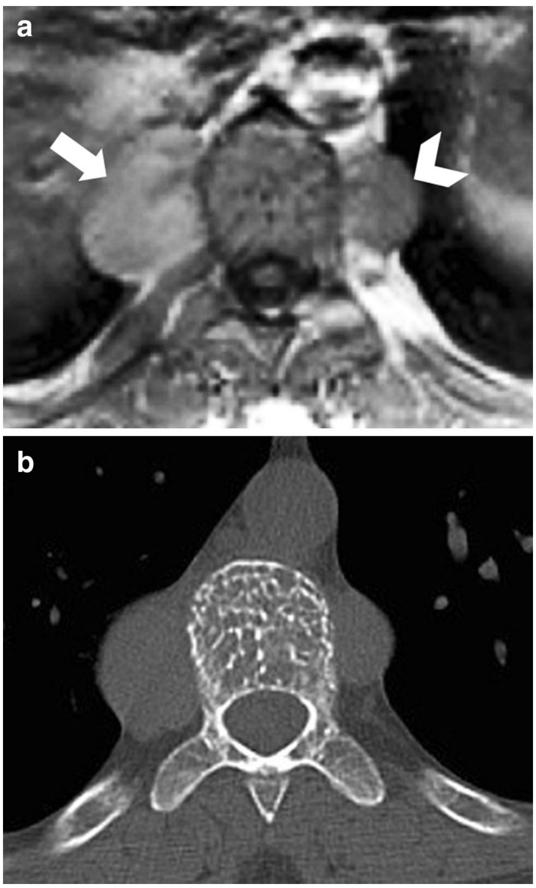

Fig. 1 Twenty-four-year-old man. **a** MRI obtained for liver iron overload evaluation using T2-FFE (TR = 1000; TE = 9); showing paravertebral EMH with bone expansion, CBI score of 1; the EMH on the right (*arrow*) has relatively homogeneous predominantly fat signal (Fat score 3), and the EMH on the left (*arrowhead*) shows rather homogeneous red marrow signal, iso-intense to the bone marrow (Fat score 0). **b** CT scan of the spine performed 3 years earlier, more superior cuts showing thoracic vertebral body expansion with cortical irregularities and erosions, along with surrounding soft tissue lesions due to EMH

was predominantly isointense to red marrow (intermediate to low signal) with some fat signal (Figs. 4, 6). A score of 2 demonstrated similar proportions of fat and red marrow signal (Figs. 3, 4, 7), and a score of 3 representing predominantly fat-containing lesion, similar to fatty bone marrow (Figs. 1a, 5a, 6).

Homogeneity score

The soft tissue lesions were classified as either homogeneous or heterogeneous based on their signal intensity on MRI. A score of 1 was for homogeneous masses (Figs. 1, 2, 3, 5, 6), and a score of 2 was for heterogeneous masses (Figs. 3, 4, 6, 7).

Margin score

Lesion margins were classified on MRI into either well defined or not well defined. The former lesions have regular contours throughout, with a score of 1 (Figs. 1, 2, 3, 5, 6). The latter lesions have at least partly irregular contour, with a score of 2 (Fig. 4, 7). If a lesion showed areas with both scores, it was considered to have a score of 2.

Bone marrow signal score (BMS)

Bone marrow MR signal was classified into red marrow, with a score of 1 (Figs. 1, 2, 3, 4, 6, 7), or fatty marrow with a score of 2 (Fig. 5a).

Statistical analysis

Data were prepared as frequencies and percentages. All bivariate comparisons were evaluated using the

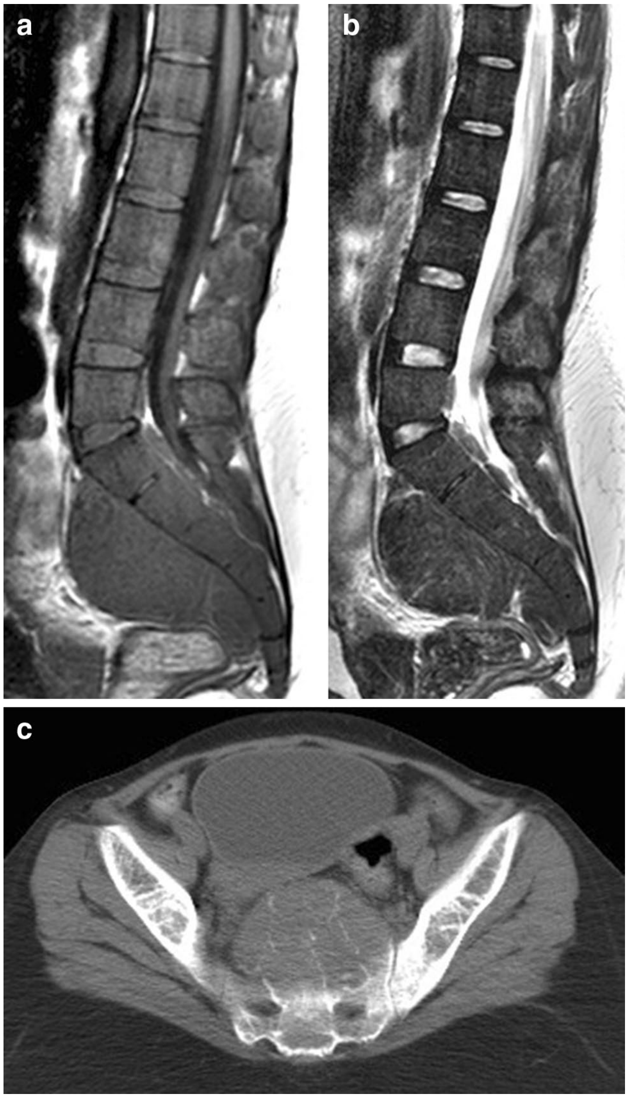

Fig. 2 Twelve-year-old girl. **a** Sagittal T1-weighted (TR = 500; TE = 15), and **b** T2-weighted MR images (TR = 3000; TE = 100). Large pre-sacral lesion showing iso-signal to bone marrow on both sequences. The sacrum is expanded but not grossly interrupted. **c** Axial CT scan however clearly identified anterior cortical invasion (CBI score 2) with large pre-sacral soft tissue structure containing sheaths of bone trabeculae and representing EMH

independent-samples *t*-test for continuous variables and the Fisher's exact and Spearman's test for categorical variables. Logistic regression analysis was used to assess for variables that were independent risk factors for the development of CBI. All *P* values are two-tailed with the level of significance set at <0.05. Statistical methods were performed using the Statistical Package for the Social Sciences (SPSS) version 19.0 (New York, USA).

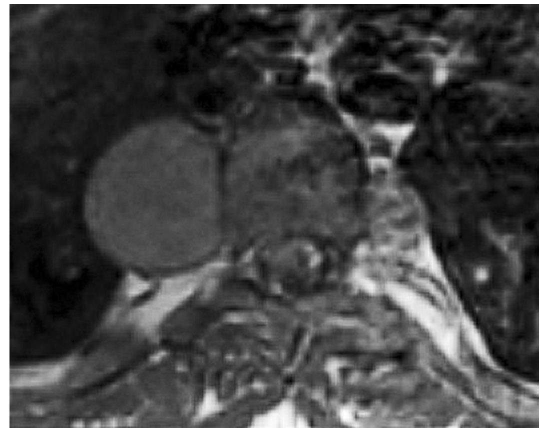

Fig. 3 Thirty-three-year-old man. T2-FFE (TR = 1000; TE = 18); bilateral paraspinal lesions. The right lesion is large and homogeneously of low signal, (iso-intense to red marrow (Fat score 0). This has CBI score of 1. The left lesion is small and heterogeneous with similar proportion of fat and red marrow signal (Fat score 2). The underlying cortex is irregular in keeping with CBI score of 2

Fig. 4 Twenty-two-year-old man. T2-FFE (TR = 1000, TE = 6); bilateral rather heterogeneous paraspinal lesions with cortical irregularity (CBI score 2). The left paraspinal lesion shows predominantly red signal similar to the bone marrow (Fat score 1). It has focal irregular contour both anteriorly and posteriorly (*arrowheads*) (Margins score 2). The right paraspinal lesion has relatively similar proportions of fat and red marrow signal (Fat score 2)

Results

Patients' characteristics

A total of 57 patients who fit the diagnosis of NTDT, with available imaging studies and laboratory values, were

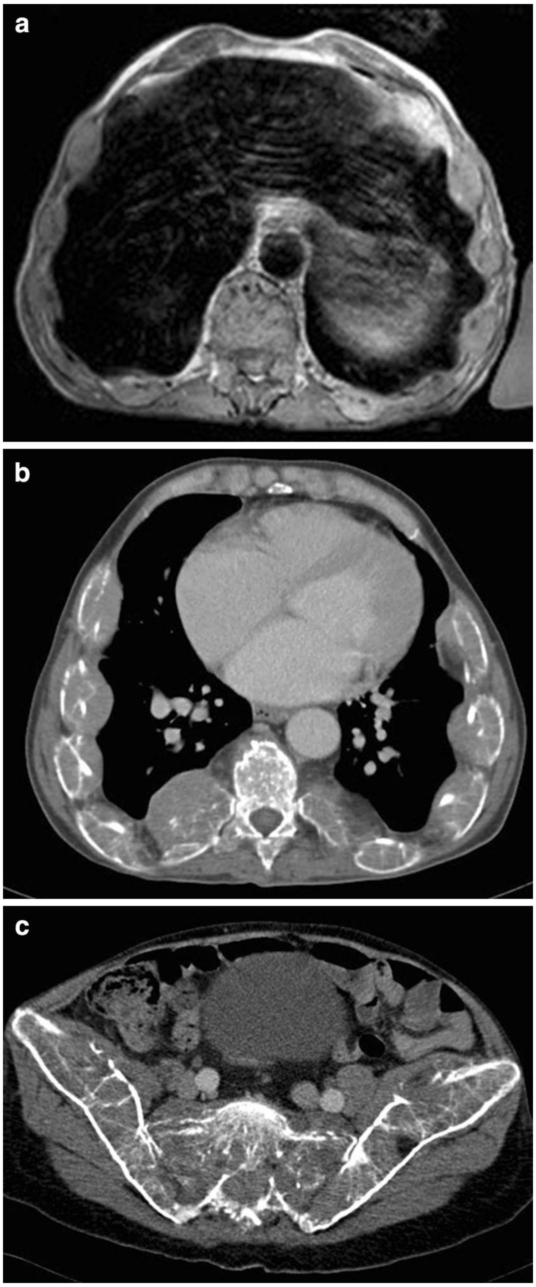

Fig. 5 Fifty-year-old man. **a** Axial T2-weighted MR image (TR = 2500, TE = 9) of the lower chest shows expansion of multiple ribs with surrounding soft tissue lesions due to definite CBI (score 2) and secondary EMH. The lesions are of homogeneous increased signal appearing isointense to bone marrow and subcutaneous tissue, in keeping with fat signal. **b** CT scan of the chest clearly showing ribs expansion, cortical invasion, and secondary EMH. **c** Pelvic CT scan showing similar sacral and bilateral iliac bones expansion with CBI and EMH

Fig. 6 Thirty-five-year-old man. MR examination using T2-FFE (TR = 1000, TE = 15); bilateral paraspinal lesions with CBI score of 2. The right lesion (*arrow*) is heterogeneous and predominantly iso-intense to red marrow as seen in the vertebra (Fat score 1). The left lesion (*arrowhead*) is rather homogeneous with a Fat score of 3, being predominantly fatty. All lesions are well defined

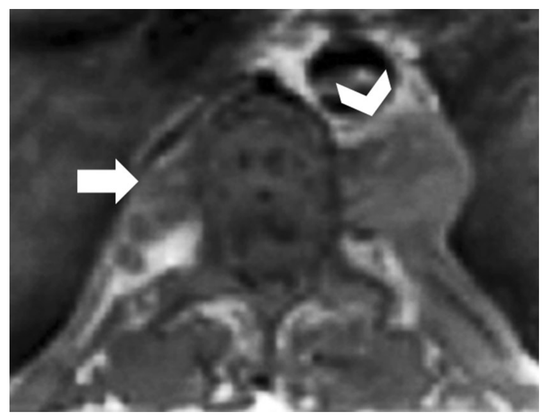

Fig. 7 Twenty-nine-year-old man. T2-FFE (TR = 1000, TE = 12), axial MR image obtained at the level of a thoracic disk space shows left paraspinal lesion appearing heterogeneous with both red and fat signal intensity (Fat score 2). It shows slight irregular contour anteriorly (*arrowhead*). The CBI score was 1. Focal right paraspinal soft tissue thickening was present (*arrow*), probably representing an early EMH formation

included in the analysis (Table 2). The mean age was 31 years (SD = 12 range, 10–65). The male-to-female ratio was 1.6:1 (35 males/22 females). Two-thirds (66.7 %) were occasionally transfused while 26.3 % were never transfused and only four patients (7 %) were regularly transfused. The mean total hemoglobin was 8.34 g/dL ± 1.77, and mean fetal hemoglobin was 68.1 ± 190.6.

Imaging analysis

Of the 57 patients, 27 (47.4 %) had a CBI score of 1 or 2. Among these, 26 were splenectomized, 14 had a CBI score of 2 (definite CBI), and 13 had CBI score of 1. All the latter patients, however, had bone marrow expansion with adjacent secondary soft tissue formation; hence, all were

Table 2 Patients' characteristics

Age (years), mean (SD)	31 (12)
Sex *n* (%)	
Male	35 (61.4)
Female	22 (38.6)
Transfusion history, *n* (%)	
None	15 (26.3)
Occasionally transfused	38 (66.7)
Regularly transfused	4 (7)
Splenectomized *n* (%)	
Yes	45 (78.9)
No	12 (21.1)
Total hemoglobin (g/dL), mean (SD)	8.34 (1.77)
Fetal hemoglobin (%), mean (SD)	68.1 (181.94)
Platelet count ($\times 10^6$/L), mean (SD)	742,339 (358,689)
Serum ferritin (ng/mL), mean (SD)	1110.82 (846.11)
Liver iron concentration	9.12 (7.04)
Morbidity *n* (%)	
CBI	27 (47.4)
Extraskeletal EMH	11 (19.3)

SD standard deviation, *CBI* cortical bone invasion, *EMH* extramedullary hematopoiesis

Table 3 Imaging results in patients with positive findings

Score	*N*	%
CBI		
1	13	48.2
2	14	51.8
BM expansion	27	100
Fat score		
0	5	18.6
1	9	33.3
2	4	14.8
3	9	33.3
Homogeneity		
1	19	70.3
2	8	29.7
Margins		
1	24	88.9
2	3	21.1
BMS		
1	18	66.7
2	9	33.3

CBI cortical bone invasion, *BM* bone marrow, *BMS* bone marrow signal

judged positive for CBI. The majority of patients had CBI at multiple sites, most commonly at the thoracic paraspinal area near the costovertebral junctions seen in 25 patients (92.6 %) (Figs. 1, 4, 6, 7). Other areas included the ribs in 6 patients (22.2 %) (Fig. 5) and both the sacrum and iliac bones in 2 patients (7.4 %) (Figs. 2, 5c). No lesions were encountered within the spinal canal.

With regard to the fat score, five contained soft tissue isointense to red marrow but no fat (0), nine were primarily composed of non-fatty soft tissue (1), four had similar proportions of fat and soft tissue isointense to red marrow (2), and nine were primarily composed of fat (3). Eight had an overall heterogeneous composition (2), while 19 were rather homogeneous (1). Three did not have well-defined margins (2), and 24 had well-defined margins (1). Eighteen had predominant red bone marrow signal (1) while nine had fatty bone marrow signal (2). The imaging scoring results are summarized in Table 3.

The remaining 30 patients had a CBI score of 0. Nineteen were splenectomized, 11 had red bone marrow signal (BMS) (1), and 19 had fatty BMS (2). Sixteen patients had mild bone marrow expansion.

Among the four patients imaged with CT scans, one had a large sacral CBI with EMH, one had similar but diffuse skeletal changes involving the ribs, spines, and iliac bones, and another had a paravertebral location of EMH.

CBI-positive versus CBI-negative patients

Table 4 summarizes the findings comparing clinical variables of CBI-positive (CBI score of 1 or 2) and CBI-negative (CBI score of 0) patients. Overall, there was no difference in age or sex between CBI-positive and CBI-negative patients ($p = 0.819$). Those with CBI were more likely to be occasionally transfused and less likely to have never been transfused ($p = 0.008$). They were also more likely to be splenectomized ($p = 0.002$), have lower total hemoglobin ($p < 0.0001$), and a higher platelet count ($p = 0.001$). There was a tendency toward lower fetal hemoglobin levels, but this did not reach statistical significance ($p = 0.258$). No significant differences were noted in serum ferritin levels and liver iron concentrations between the two groups. Logistic regression analysis to correct for possible confounders showed that splenectomy and a lower hemoglobin level were the only two independent risk factors for the development of CBI (Table 5).

Discussion

In the present study, almost half of NTDT patients imaged for various purposes had evidence of CBI with EMH. These patients were more likely to be splenectomized and have a lower hemoglobin level. The scoring system provided a systematic approach, which allowed us to better describe

Table 4 Comparison of patients with and without CBI

Parameter	Cortical bone invasion (CBI)		*P* value
	Yes	No	
Age (years), mean (SD)	30 (11)	31 (13)	0.635
Sex, *n*			
Male	17	18	0.819
Female	10	12	0.819
Transfusion history, *n*			
None	2	13	0.004
Occasionally transfused	23	15	
Regularly transfused	2	2	
Splenectomized, *n*			
Yes	26	19	0.002
No	1	11	0.002
Total hemoglobin (g/dL) mean, (SD)	7.39 (1.10)	9.19 (1.84)	<0.0001
Fetal hemoglobin (%), mean (SD)	40.4 (22.1)	93.1 (249.2)	0.258
Platelet count ($\times 10^6$/L), mean (SD)	901,753 (355,571)	598,866 (300,227)	0.001
Serum ferritin (ng/mL), mean (SD)	1247.24 (188.87)	988.29 (697.15)	0.261
Liver iron concentration	10.23 (7.64)	8.12 (6.42)	0.267
Morbidity, *n*			
EMH Yes	7	4	0.229
No	20	26	0.229

SD standard deviation, *EMH* extramedullary hematopoiesis

Table 5 Logistic regression for factors independently affecting CBI status

	p value	OR	95 % CI	
			Lower	Upper
Splenectomy	0.003	92.974	4.646	1860.653
Hemoglobin	0.002	0.257	0.109	0.608
Constant	0.017	1187.792		

OR odds ratio, *CI* confidence interval

this entity so that it can be recognized when imaging findings are suggestive.

Historically, EMH was an autopsy diagnosis. It was not until 1945 that Ask-Upmark diagnosed paraspinal EMH by roentgenograms and antemortem biopsy [11]. The first documented case diagnosed by fine needle aspiration biopsy was in 1951 by Hanford et al. [12]. An accurate early diagnosis of spinal EMH is necessary, especially in patients facing serious neurological compromise. It might represent a difficult diagnosis, especially when the location, distribution, and size of the masses raise the possibility of other differential diagnoses, such as lymphomas and primary bone tumors [13]. In most of the reported cases in the literature, tissue biopsy or surgical resection was needed; however, these procedures carry a risk of hemorrhagic complications particularly that the lesions are usually highly vascular [14]. When characteristic imaging findings are recognized in patients with NTDT as CBI, invasive diagnostic procedures, such as biopsies, are not necessary.

Currently, MRI is the modality of choice in evaluating patients with EMH in thalassemia. Masses in the spine appear heterogeneous when they are mixed with the epidural fat and homogenous when they replace it completely [13, 15]. The lesions are usually characterized by lobular masses with increased signal intensity when compared to that of the red marrow in the adjacent vertebral bodies, on T1-weighted and T2-weighted images [16]. Exceptionally, they appear isointense on T2-weighted images when excessive iron is present in the erythroid tissue [16]. Usually, the lack of enhancement post-gadolinium administration helps its differentiation from other lesions such as abscesses, primary bone tumors, or metastases [17]. In the present study, MRI was essential in the diagnosis of CBI by showing soft tissue lesions adjacent to expanded bone marrow and cortical irregularity. However, CT scan is accurate in differentiating between probable and definite CBI, since cortical breaks are, as expected, not always easily apparent on MR images and much better seen on CT scan. Approximately two-thirds of our patients showed predominant red bone marrow signal due to anemia, the same number had homogeneous soft tissue lesions, and all but three had well-defined margins. Hence, in the clinical setting of NTDT, expanded red bone marrow along with cortical irregularity associated with adjacent well defined, mostly homogenous, soft tissue lesions showing either predominant isointense signal to red marrow or predominant fatty signal would be highly suggestive of CBI with secondary EMH. There was, however, variable composition of the soft tissue lesions regarding the proportion of fat and did not parallel the signal intensity of bone marrow. Threshold values for our scoring system that resulted from these findings were not analyzed since the variable appearance of these lesions may lead to variable scoring, rendering such values of limited use. The importance of this scoring system was to provide a systematic approach to interpret and recognize the variable appearances of these lesions.

The most common site of CBI in our study was the thoracic spine, at the costovertebral junction, whereby it was seen in over 90 % of patients, followed by the ribs. These data differ from a previous clinical and radiographic study on EMH, which found that the most common musculoskeletal location is the ribs, followed by the vertebrae [18]. This may be due to the fact that we did not have complete thoracic imaging for all patients, which may have underrepresented the number of rib lesions.

Patients with positive findings of CBI in the present study were more likely to have undergone a splenectomy, and have lower hemoglobin and a higher platelet count. To note that in the multivariate analysis platelet count was found to be a confounder associated with splenectomy. Previous studies have shown that other complications related to NTDT such as venous thromboembolism are also associated with splenectomy and a higher platelet count [19]. Splenectomy is also associated with increased risk of infection and pulmonary hypertension.

A recent prospective study found that serum transferrin levels could be predictive of EMH in splenectomized patients [20]; however, this was not found to be predictive of CBI in our study. Previous data on EMH in NTDT found transfusion to be protective; however, this was not the case in our study [19]. Those with positive findings of CBI in the present study were less likely to never have been transfused and much more likely to have been occasionally transfused than those with negative findings. However, in our logistic regression analysis, transfusion was shown to be a confounder linked to the level of hemoglobin in our patients. In fact, lower hemoglobin levels increased the likelihood of having CBI, which can explain their increased transfusion requirements.

Tsitouridis et al. evaluated CT and MRI findings of paraspinal EMH in patients with thalassemia [21]. Their patient population included both NTDT and thalassemia major, whereas our patient population comprised only NTDT. They did not find evidence of CBI in their patient population and reported that paraspinal EMH was found at variable distance from the cortex. Another series reported that the paravertebral masses did not "usually" extend by erosion of the cortex from the intramedullary space [15]. Tsitouridis et al. hypothesize that penetrating vessels from the vertebral cortex may possess an ability to produce red blood cells. This raises the possibility that two different processes take place in the development of paraspinal EMH, one that results from CBI and the other, which may be related to penetrating vessels from the vertebral body. Although this theory may be valid, we did not however encounter in our series any case of paraspinal masses adjacent to normal bone or any lesion away from bone. One explanation of this difference in our findings is that the slice thickness of the CT scan used in the Tsitouridis study was 5 mm with no high bone window resolution whereas the slice thickness in our study was 1.5 mm. Penetrating vertebral vessels might contribute to this phenomenon along with the presence of cortical invasion as seen in our series.

This study has limitations inherent to all retrospective studies. Imaging studies available were performed for other purposes and were not uniform in modalities or body parts imaged. Therefore, some instances of CBI may have been missed. Additionally, the lack of CT scans in many patients made the diagnosis of cortical disruption difficult in some cases. However, this study relied mainly on MR features. Furthermore, clinical data, which had been gathered prospectively on this patient population for a previous study and was readily available, were missing history on pulmonary hypertension, hydroxyurea intake, and laboratory data such as nucleated red blood cells.

In conclusion, our data suggest that CBI and secondary EMH are common findings in patients with NTDT. We found that splenectomy and lower hemoglobin were independent risk factors for its development. The majority of the extramedullary lesions were well defined, homogenous, showing either minimal or significant amount of fat, and mainly located at the costovertebral junction of expanded thoracic vertebral bodies, rich in red marrow. The described imaging findings are helpful in the accurate diagnosis, distinguishing CBI from skeletal tumors, hence precluding unnecessary interventions such as biopsies. Further prospective studies are needed to confirm these findings, validate the scoring system, and better characterize this entity.

Compliance with ethical standards

Conflict of interest Karim Masrouha declares that he has no conflict of interest, Joelle Wazen declares that she has no conflict of interest, Anthony Haddad declares that he has no conflict of interest, Fadi Saadeh declares that he has no conflict of interest, Ali Taher declares that he has no conflict of interest, Nabil Khoury declares that he has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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