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Premature epiphyseal fusion and extramedullary hematopoiesis in thalassemia

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Abstract. The main skeletal abnormalities in β-thalassemia are widening of medullary spaces, rarefaction of bone trabeculae, thinning of cortical bone, and perpendicular periosteal spiculation. Premature epiphyseal fusion (PEF) and extramedullary hematopoiesis (EH) are found, though more rarely. The incidence of PEF and EH in 64 patients affected by β-thalassemia is reported. The different incidence of such complications in thalassemia major and intermedia is reported, and a possible correlation with transfusion regimen is also considered.

Key words: Premature epiphyseal fusion – Extramedullary hematopoiesis – Thalassemia – Hemoglobin synthesis – Low-transfusion regimen – Hypertransfusion regimen

Thalassemia is a disorder of hemoglobin synthesis which is characterized into major and intermedia forms by low levels of hemoglobin, hepatosplenomegaly, and skeletal alterations such as widening of the medullary spaces, rarefaction of the bone trabeculae, thinning of the cortex, and periosteal reaction with perpendicular spiculation. Premature epiphyseal fusion (PEF) and extramedullary hematopoiesis (EH) occur, though more rarely.

Severe thalassemia requires iron-chelative and transfusion therapy. Transfusions were at first limited to ensure hemoglobin levels between 4 and 6 g/100 ml (low-transfusion regimen). A hypertransfusion regimen ensuring hemoglobin levels between 8 and 10 g/100 ml was then found to give better results in reduction of hepato- and cardiomegaly and in regression of bony lesions [2, 7]. The relationship between transfusion therapy and the occurrence of PEF/EH is not clear, nor is the relative incidence of such complications in thalassemia major and intermedia.

In this paper we report the incidence of PEF and EH from our experience in dealing with 64 patients affected by β-thalassemia; the possible correlation with the transfusion regimen is discussed.

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Material and methods

Our study included 64 patients affected by β-thalassemia who have been followed in the hematological department from 1983 to 1987. Fifty-one patients 27 males and 24 females, whose ages ranged between 4 and 30 years (average 15.9 years) were affected by thalassemia major. Nine of these began a hypertransfusion regimen before 5 years of age; the remaining 42 had only been hypertransfused in the last 5 years, after a variable period of the low-transfusion regimen. The age at which the therapy was started in all cases of homozygous thalassemia ranged from 3 months to 42 months (mean value–14 months). Splenectomy was always performed. It must also be considered that the hypertransfusion regimen was only initiated in 1976–79, so that only the youngest subjects of our group have been hypertransfused since the early years of life. This series of patients has been followed radiologically with a chest radiograph every 6 months. Shoulder and knee radiographs were also taken in children of 10–13 years of age.

The remaining 13 patients, affected by thalassemia intermedia, represent a less homogeneous group, because of the variability in undergoing transfusions and, in two cases, because of the voluntary interruption of the therapy. This group consists of six males and seven females, whose ages ranged between 14 and 15 years (average 26.9 years). Almost all were able to maintain levels of hemoglobin compatible with life (6–8 g/100 ml) even without regular transfusions. Radiological examinations were limited to chest radiography, which was performed about every 12 months. The shoulders and the knees were only studied at the time of the first examination.

The therapy (low-transfusion regimen) began later than in the previous group, ranging between 4 and 28 years (mean 22 years). This was related to their relatively good health and to the satisfactory levels of hemoglobin maintained spontaneously for years.

Results

Premature epiphyseal fusion (PEF) was found in 9 of our 64 patients (14.1% or 16.3% if we consider only the 55 patients over 10 years). It involved both humeri in three cases and only one humerus in six cases. It also involved the tibia in one patient. Out of these nine subjects, six were affected by thalassemia major and three by thalassemia intermedia.

The mean age of first transfusion in patients affected by thalassemia major was about 14 months, while it was over 2 years in the six patients who presented with PEF. None of these six patients had begun a hypertransfusion regimen before 5 years of age, and none of the children hypertransfused earlier showed such skeletal complications. The mean age of first transfusion in the cases of thalassemia intermedia was about 22 years. However, only two out of the three cases that presented with PEF were transfused so late and even discontinously, while the third one unexpectedly began the transfusional therapy at only three years.

As far as extramedullary hematopoiesis (EH) is concerned, and in particular the posterior mediastinal involvement, it was only discovered in one of the 51 patients affected by thalassemia major. This patient, who had been transfused since the age of 2 years and 5 months and hypertransfused only recently, also showed unilateral premature fusion of the proximal humeral epiphysis. EH was found in 9 of the 13 patients affected by thalassemia intermedia; two of these patients also presented PEF (Table 1).

Table 1. Table of PEF and EH in correlation with transfusional therapy

Time of last X-ray	1st transfusion	1st hypertransfusion
Thalassemia major (51 cases: 24 females (F) and 27 males (M))		
PEF only		
(M) 17 years	30 months	12 years
(F) 17 years	3 months	12 years
(F) 15 years	26 months	11 years
(M) 16 years	24 months	11 years
(M) 17 years	22 months	13 years
PEF + EH		
(M) 19 years	29 months	15 years
EH only		
none		
Thalassemia intermedia (13 cases: 7 females (F) and 6 males (M))		
EH only		
(M) 45 years	38 years	none
(F) 24 years	20 years	none
(M) 22 years	19 years	none
(F) 23 years	5 years	none
(M) 36 years	28 years	none
(F) 37 years	30 years	none
(M) 42 years	33 years	none
PEF + EH		
(F) 30 years	18 years	none
(F) 33 years	27 years	none
PEF only		
(M) 14 years	3 years	none

Discussion

β-Thalassemia is a disorder of hemoglobin synthesis characterized by a decreased or absent production of globin β-polypeptide chains, which leads to ineffective erythropoiesis, severe hemolysis, and secondary anemia. The clinical forms are generally separated into the following [1, 15]:

1. Thalassemia minor (heterozygous condition or trait carriers)
2. Thalassemia intermedia (Rietti-Greppi Micheli anemia) with a clinical expression intermediate between thalassemia minor and major (which can be determined either by a homozygous thalassemia with attenuated symptoms or, more often, by double heterozygosis of β-thalassemia and other genes codifying the synthesis of β-chains)
3. Homozygous thalassemia major (Cooley disease)

Clinically in all forms there is an over-stimulation of hemopoiesis, which is responsible for hepatosplenomegaly and bony abnormalities. At present, it is generally accepted that patients affected by thalassemia major require, in addition to iron-chelation therapy, a hypertransfusion regimen, so that the hemoglobin level is maintained between 8 and 10 g/dl. This kind of therapy seems to provide better results in the reduction of hepato- and cardiomegaly and regression of skeletal alterations, when compared with the low-transfusion regimen, which only ensures hemoglobin levels between 4 and 6 g/dl [2, 7].

Both the most frequent skeletal lesions (widening of the medullary spaces, thinning of the trabeculae and of the cortex, cystic-like areas and radiating trabeculae of the skull) (Fig. 1A–D) and the less frequent ones (PEF and EH) [3, 9, 11, 14] are radiologically detectable. PEF seems to be due to the proliferating marrow perforating the cortex and expanding beneath the periosteum into the ar-

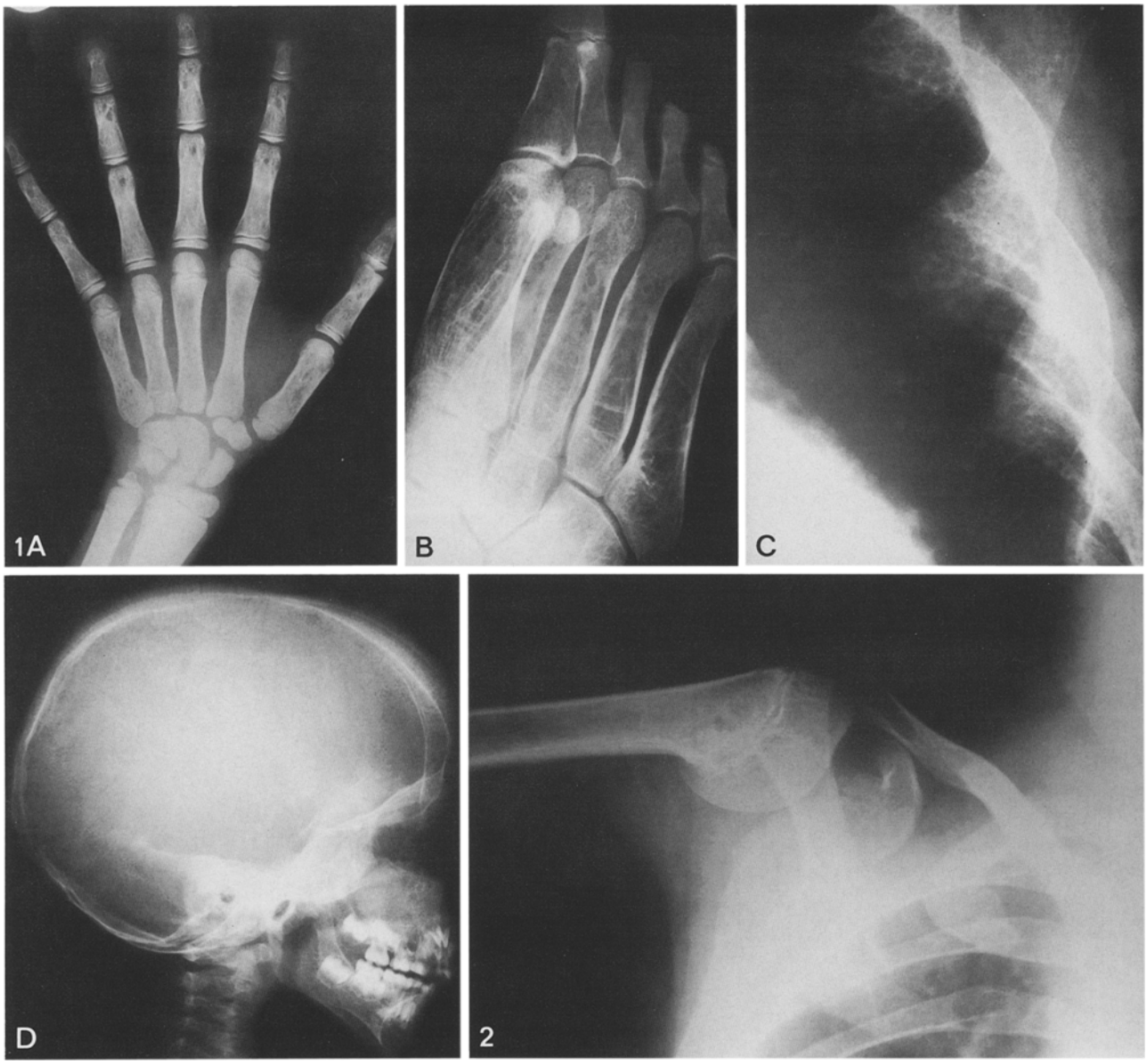


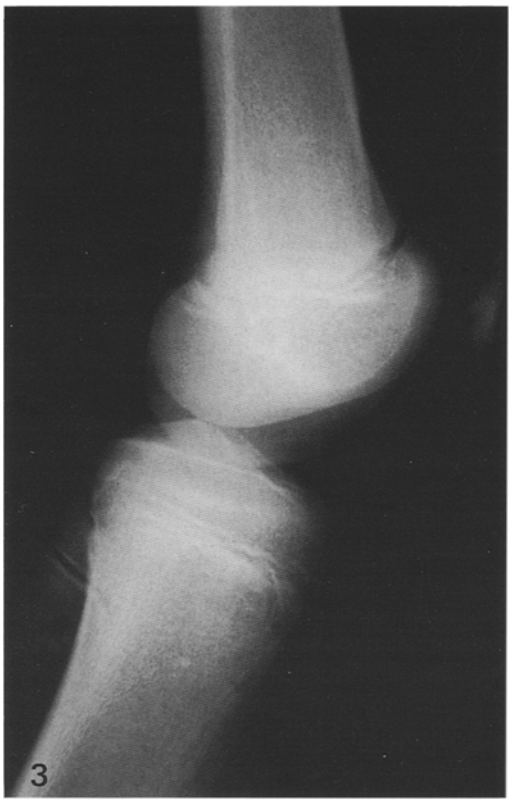
Fig. 1A–D. Main skeletal abnormalities in thalassemia major and intermedia: widened medullary spaces, thinned trabeculae and cortex, cystic-like areas (**A–C**), and vertical radiating spiculations of the skull (**D**)

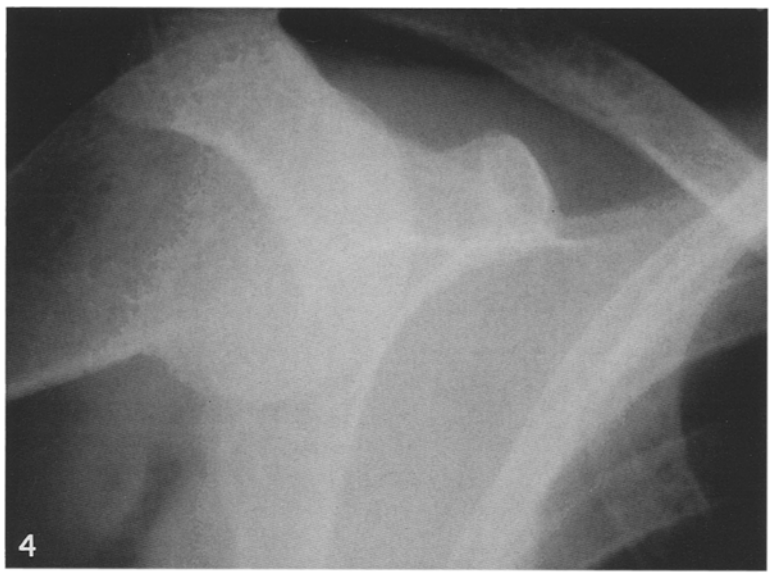
Fig. 2. Humerus varus due to premature epiphyseal fusion (PEF) with persistence of growth cartilage only on the external aspect

eas of least resistance. The most common sites of involvement are the proximal epiphysis of the humerus (Fig. 2), the distal epiphysis of the femur, and both the proximal and distal epiphyses of the tibia (Fig. 3).

The proximal humeral epiphysis is almost completely covered by musculotendinous attachments, except for its medial aspect, where the varus deformity takes place. Mechanical factors such as the normal force vectors acting on the glenohumeral joint are also implicated in this peculiar type of deformity (Figs. 4 and 5). The affected bone becomes deformed, and the articular relationship is altered.

In our experience, the incidence of PEF is higher in thalassemia intermedia than in thalassemia major, in accordance with Lawson's results [7]. However, we have found a lower prevalence than Lawson both in the major (6/51 versus 10/36) and in the intermedia form (3/13 versus 7/7). This may





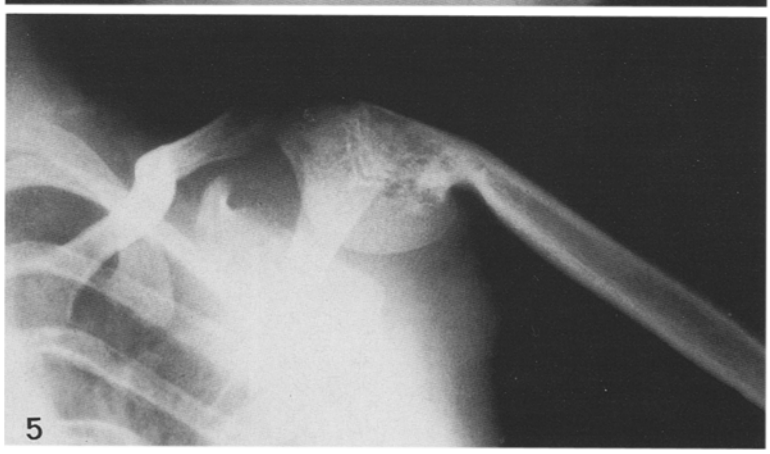


Fig. 3. PEF involving the distal end of the femur and the proximal end of the tibia with persistence of the anterior part of the growth cartilage

Fig. 4. Humerus varus with a small cortical indentation on the medial side resulting from complete fusion of the growth cartilage

Fig. 5. Severe deformity of the proximal end of the humerus with a deep notch on the medial side and varus deformity due to PEF

be due either to care in evaluating irregularities of the medial side of the proximal humeral epiphysis or to the random nature of the cases.

EH may affect the liver, the spleen, and the lymph nodes, as a compensatory response to the deficient production of blood cells by the bone marrow (e.g., as in myelofibrosis), or in masses arising from the hypertrophied marrow extruding through the bony cortex (typical of hemolytic anemias) (Fig. 6A, B), more often appearing as well-defined bilateral paravertebral masses causing enlargement of the posterior mediastinum [1, 4, 5, 8, 10–12] (Fig. 7A, B).

The incidence of EH is clearly higher in thalassemia intermedia than in thalassemia major (9/13 versus 1/51), and this is in accordance with Korsten's results (eight cases out of ten who presented with EH were affected by thalassemia intermedia) [6].

A careful analysis of these data highlights the following points which still need to be explained: 1) Why are PEF and especially EH mainly observed in thalassemia intermedia rather than in thalassemia major 2) Why may one or both these complications take place in a particular individual?

We believe that the greater incidence of PEF and especially of EH in the intermediate form may be related to the fact that these patients are mostly able to maintain an adequate hemoglobin concentration, rarely requiring early and long-lasting transfusion therapies. As a consequence, the epiphyseal fusion generally takes place before the beginning of therapy, as the hyperplastic marrow damages the growth cartilage and invades the subperiosteal space, with subsequent varus deformity of the humeral head. Once the epiphyses have fused, the hyperplastic marrow cannot significantly alter the bone structure of these sites any more.

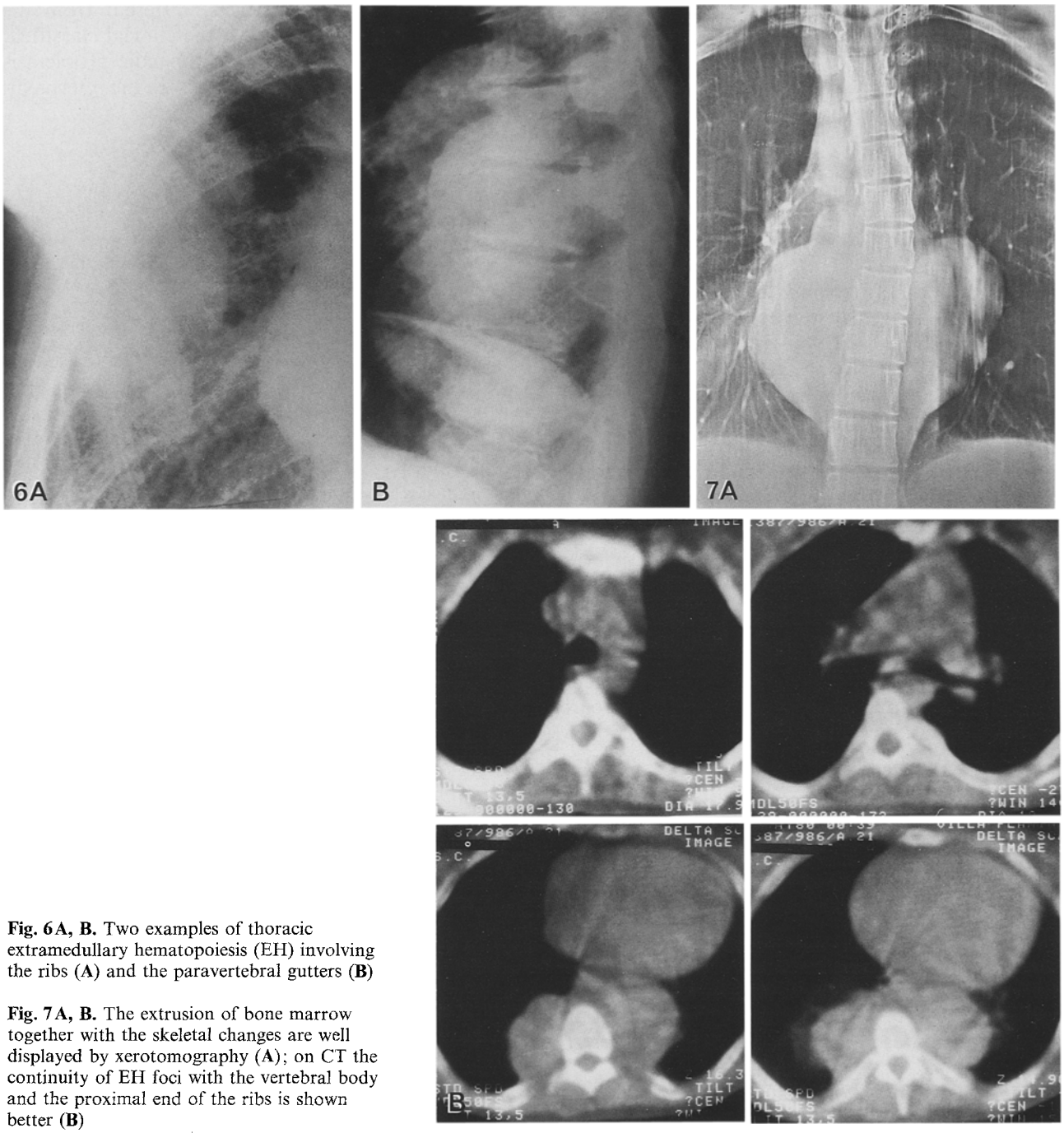


Fig. 6A, B. Two examples of thoracic extramedullary hematopoiesis (EH) involving the ribs (**A**) and the paravertebral gutters (**B**)

Fig. 7A, B. The extrusion of bone marrow together with the skeletal changes are well displayed by xerotomography (**A**); on CT the continuity of EH foci with the vertebral body and the proximal end of the ribs is shown better (**B**)

Instead, masses of EH are located at the paraspinal gutters and rib expansion can occur (Fig. 2). The EH therefore has a later time of onset and is more frequently observed than PEF. In the intermediate form, hypertrophy of the marrow has much more time to develop and the bone marrow can be extruded through the thinned cortex and the trabeculae of the adjacent ribs. This is in accordance with the data reported in the literature [1, 6, 12, 13].

On the other hand, in thalassemia major, the early and regular transfusions mitigate the severe anemia, so that the bone marrow is less aggressive near the unfused growth cartilages and the heterotopic bone marrow formation is reduced. Also the limited life expectancy of these subjects contributes to a reduction of these bone alterations, which need quite a long time to develop.

We have examined our patients with PEF and

EH in order to determine any possible relationship between these two complications and their pathogenetic mechanism. In our opinion, the presence of PEF without EH in five patients affected by thalassemia major is understandable since a transfusion therapy set up after the second year of life may not be sufficient to prevent bone marrow from damaging the growth cartilages, while it can avoid the development of EH masses. This was also demonstrated by the absence of EH in 50 out of 51 subjects in our study. The only patient who showed EH had been started both on a low-transfusion and on a hypertransfusion regimen later than the others (at 2.5 years and 15 years respectively). In addition, the presence of EH without PEF is understandable in seven patients affected by thalassemia intermedia since in these cases the marrow hypertrophy is generally not severe enough to injure the growth cartilages in childhood, when they are vulnerable. On the other hand, the bone marrow is not sufficiently restrained by the transfusions and has more time to produce masses of EH.

However, other cases are not so easily understandable. In two cases of thalassemia intermedia, both PEF and EH were observed. Both subjects began transfusions quite late (at 18 and 27 years respectively). It is possible that the unexpected finding of PEF may be explained with some early and asymptomatic increase of marrow activity. Another patient affected by thalassemia intermedia, although started early on transfusional therapy, presented with PEF. EH was not demonstrated, perhaps due to the young age of the patient (13 years). One further patient affected by thalassemia intermedia, who was also managed with early transfusions, presented with EH at the age of 22 years. These cases may represent an intermediate form of the disease with a genetic expression similar to the major form, so that the low-transfusion regimen would be insufficient to prevent occasional and unrecognised episodes of marrow hypertrophy.

We believe that the classification of thalassemia into major and intermediate forms, though clinically useful, is not sufficient to include all the possible variants of genetic expression, and probably some cases require a therapy different from the one expected on the basis of the clinical classification. The most important orthopaedic problem is that of preventing PEF, especially in the intermediate form.

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