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Pictorial review

Imaging features of thalassemia

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Abstract. Thalassemia is a kind of chronic, inherited, microcytic anemia characterized by defective hemoglobin synthesis and ineffective erythropoiesis. In all thalassemias clinical features that result from anemia, transfusional, and absorptive iron overload are similar but vary in severity. The radiographic features of β-thalassemia are due in large part to marrow hyperplasia. Markedly expanded marrow space lead to various skeletal manifestations including spine, skull, facial bones, and ribs. Extramedullary hematopoiesis (ExmH), hemosiderosis, and cholelithiasis are among the non-skeletal manifestations of thalassemia. The skeletal X-ray findings show characteristics of chronic overactivity of the marrow. In this article both skeletal and non-skeletal manifestations of thalassemia are discussed with an overview of X-ray findings, including MRI and CT findings.

Key words: Thalassemia – Extramedullary hematopoiesis – MRI – CT

Introduction

Thalassemia, which was described in 1927 by Cooley et al., is a kind of severe anemia associated with splenomegaly and bone abnormalities [1]. The thalassemias are hereditary anemias that occur because of mutations that affect the synthesis of hemoglobin and is typically seen in Mediterranean countries. Thalassemias can be classified according to the chain involved. In β-thalassemia there is deficient synthesis of β-globin, whereas in α-thalassemia there is deficient synthesis of α-globin. Reduced synthesis of one of the two globin polypeptides leads to deficient hemoglobin accumulation, resulting in hypochromic and microcytic red cells. Severe β-thalassemia, which is also termed Cooley's anemia, is characterized by severe anemia, growth abnormalities, hepatosplenomegaly, bone deformities, dysfunction of almost all organ systems, and iron overload. Because both β genes are abnormal, very little or no β-chain synthesis occurs, and the excess of insoluble α-globin chains in the red cells leads to intracellular precipitation that affects both erythropoiesis and red cell life span. The resulting ineffective erythropoiesis causes osteoporosis, extreme expansion of marrow space in the long bones, skull, and facial bones, as well as the development of extramedullary hematopoiesis (ExmH) in the liver, spleen, and around spinal vertebrae.

Clinical classification of β-thalassemia is based on the severity of the anemia and includes thalassemia major, intermedia, and minor. Those with thalassemia major have an absolute requirement for blood without which severe anemia leads to death in infancy or early childhood. In contrast, patients with thalassemia intermedia are able to maintain their hemoglobin level at 6–7 g/dl without transfusion. This level is compatible with fairly normal growth, and many of these patients survive into adulthood. Individuals with thalassemia minor are asymptomatic and anemia is very mild, if present.

Skeletal manifestations

The changes present in the skeletal system are the result of marrow hyperplasia in response to chronic anemia. The skeletal response to this marrow proliferation consists of expansion of the medulla, thinning of the cortical bone, and resorption of the cancellous bone, resulting in a generalized loss of bone density.

Spine

Marked osteoporosis and cortical thinning may predispose to compression fracturing of the vertebra (Fig. 1).

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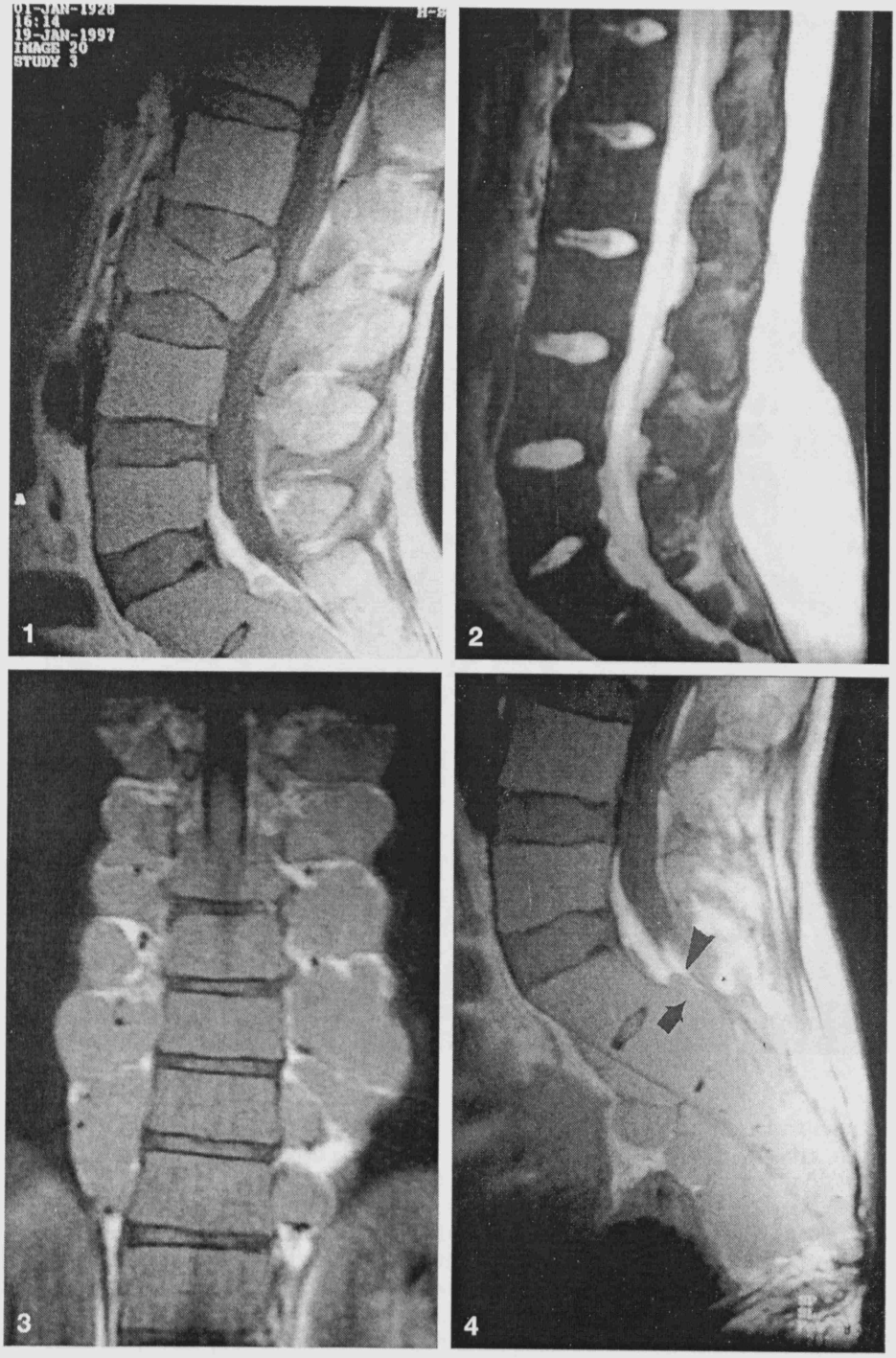


Fig. 1. A 67-year-old patient with thalassemia intermedia. T1-weighted turbo-spin-echo [TSE; TR/TE = 880/15 ms, echo train length (ETL) = 6] sagittal image showing lumbar vertebra with intermediate signal intensity within marrow and compression fracture in the corpus of L3 vertebra. Also note the anterior epidural extension of extramedullary hematopoiesis (ExmH) along the posterior border of sacrum

Fig. 2. A 20-year-old female with thalassemia intermedia. T2-weighted TSE (TR/TE = 5000/119 ms, ETL = 6) sagittal image shows the low signal intensity of lumbar vertebrae due to transfusional iron deposition

Fig. 3. A 40-year-old patient with thalassemia intermedia. T1-weighted TSE (TR/TE = 786/17 ms, ETL = 6) coronal image demonstrates multiple paravertebral masses caused by ExmH

Fig. 4. A 67-year-old patient with thalassemia intermedia (same patient as in Fig. 1). A T1-weighted TSE (TR/TE = 786/17 ms, ETL = 6) sagittal image showing the anterior epidural *(arrowhead)* and presacral soft tissue masses caused by ExmH. Note the cortical destruction along the posterior border of sacral vertebrae *(arrow)*

The MRI appearance of marrow in thalassemia is a reflection of transfusion and chelation therapy [2]. Iron deposition may occur in active red marrow regions despite chelation therapy (Fig. 2). In thalassemia, posterior paravertebral, mediastinal, or presacral masses represent sites of ExmH resulting from extraosseous extension of medullary tissue (Fig. 3) [3]. Epidural extension due to ExmH may also be seen in thalassemia patients and may cause cord compression [4] (Fig. 4). Platyspondyly is another spinal manifestation seen in hypertransfused thalassemic patients [5].

Skull and facial bones

Skull changes consist of the widening of diploic spaces and displacement and thinning of the outer table. Sometimes the diploic trabeculae orient themselves perpen-

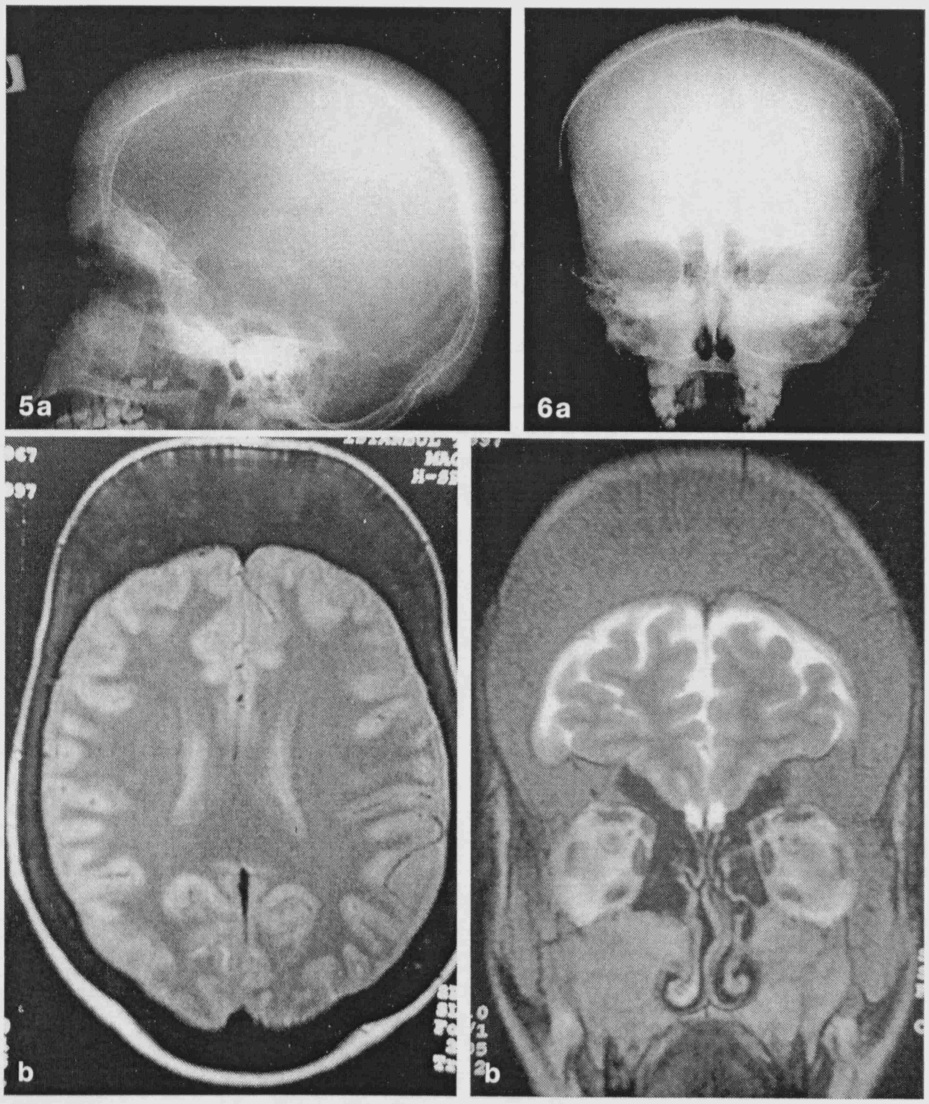


Fig. 5a, b. A 19-year-old patient with thalassemia major. **a** Skull radiography demonstrating the "hair-on-end" appearance; **b** Proton-density-weighted TSE axial MR image (TR/TE = 3700/17 ms, ETL = 6) reveals widened diploic space most prominently in the frontal bone

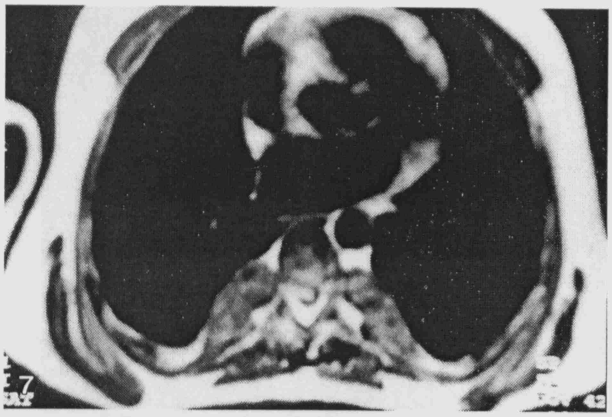
Fig. 6a, b. A 12-year-old patient with thalassemia major. **a** Plain skull film shows loss of the maxillary sinus aeration. **b** T2-weighted TSE (TR/TE = 5000/119, ETL = 6) coronal image of another patient with thalassemia intermedia showing the obliteration of the maxillary sinus by soft tissue

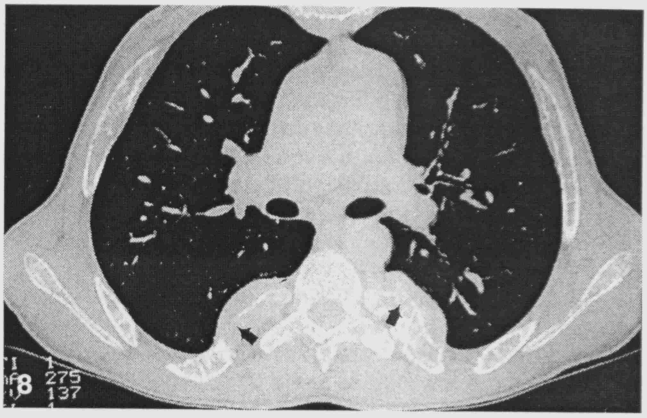
dicular to the tables producing a radial pattern called "hair-on-end" appearance (Fig. 5). Widened diploic space is hypointense to gray matter on T1, T2, and proton-weighted images. Overgrowth of marrow in frontal, temporal, and facial bones consistently impedes pneumatization of paranasal sinuses (Fig. 6). Marrow overgrowth in the maxillary bone may cause lateral displacement of the orbits and leads to ventral displacement of central incisors producing the "rodent facies" which is pathognomonic for thalassemia.

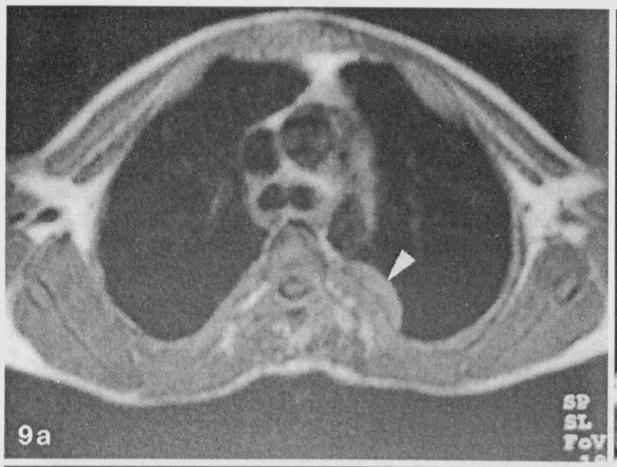
Ribs

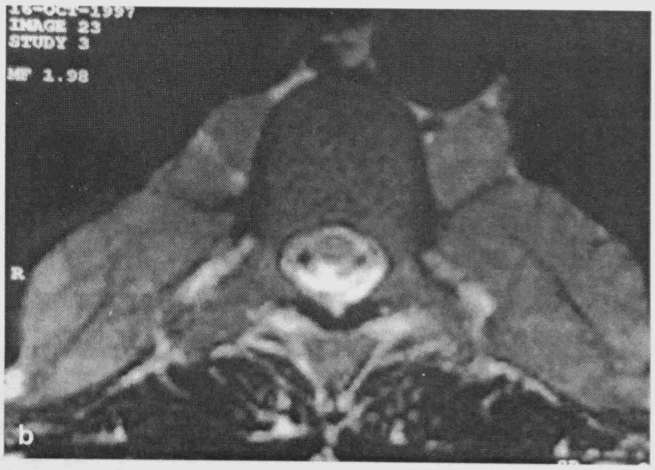
Several abnormalities are seen in the ribs [6]. Markedly expanded head and neck regions of ribs at the sites of attachment to the vertebral column are usual findings of thalassemia (Fig. 7). Expansion of the hematopoietic tissue in the marrow space leads to permeative erosions of the inner cortex (Fig. 8). Through these erosions hematopoietic tissue bulges outward leading to ExmH occurring mostly in the posterior segments of the ribs and producing posterior mediastinal soft tissue masses (Fig. 9). Extramedullary hematopoiesis is seen in different forms varying from minimal soft tissue masses anterior to the posterior parts of the ribs to extensive posterior mediastinal masses.

Other findings include osteoporosis, localized lucencies due to hyperplasia of marrow within the medulla, rib-within-a-rib appearance, and subcortical lucency. Rib-within-a-rib appearance is particularly seen in the mid and anterior portions of the ribs. Hypertrophied marrow perforates the cortex and extends longitudinally beneath the periosteum cloaking the original developing rib resulting in the rib-within-a-rib appearance. Thus, the central area of the medulla shows increased density and is separated from the superior and inferior cortices of the ribs by medulla of normal or decreased density (Fig. 10).









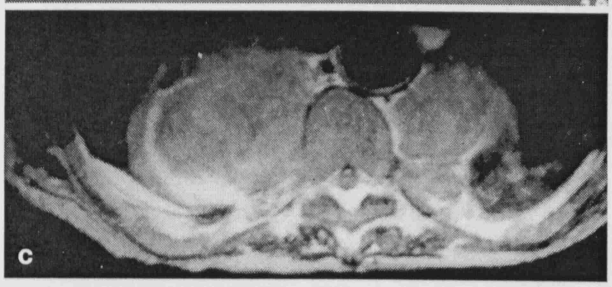


Fig. 7. A 30-year-old patient with thalassemia major. T1-weighted SE (TR/TE = 770/15 ms) axial MR images reveal expansion in head and neck region of the ribs

Fig. 8. A 40-year-old female with thalassemia intermedia. Axial CT image showing the cortical erosions *(arrowheads)*, also are seen osseous medullary expansions

Fig. 9a–c. Magnetic resonance images demonstrating the rib changes and ExmH. **a** A 27-year-old patient with thalassemia intermedia. T2-weighted TSE (TR/TE = 6915/90 ms, ETL = 6) axial MR image demonstrating early ExmH lesion located anteriorly to the rib *(arrowhead)*. **b** A 40-year-old patient with thalassemia intermedia. T2-weighted TSE (TR/TE = 4300/119 ms, ETL = 6) image demonstrating bilateral soft tissue masses located anterior to the ribs reflects the ExmH. Also seen are the bilateral paravertebral masses. **c** A 67-year-old patient with thalassemia intermedia. T1-weighted SE (TR/TE = 770/15 ms) image demonstrating advanced stage of ExmH with huge posterior mediastinal masses

Vascular impressions

Hematopoietic marrow is a very vascular structure and marrow proliferation is associated with increase in blood supply, and this is demonstrated roentgenographically as enlargement of the nutrient foramina of the tubular bones.

Metaphyseal abnormalities

Premature fusion of the growth plates in the tubular bones of the extremities represents a common finding in children with thalassemia major [7]. This finding, which has been noted in 10–15% of patients, generally occurs after the age of 10 years and is most frequent in the proximal humerus and distal femur. It occurs most commonly in patients who are not transfused until late childhood or adolescence. Also some morphological changes may be seen in the metaphysis of long bones as a result of deferoxamine therapy [8].

Non-skeletal manifestations

Extramedullary hematopoiesis

Extramedullary hematopoiesis represents the body's attempt to maintain erythrogenesis when there is an im-

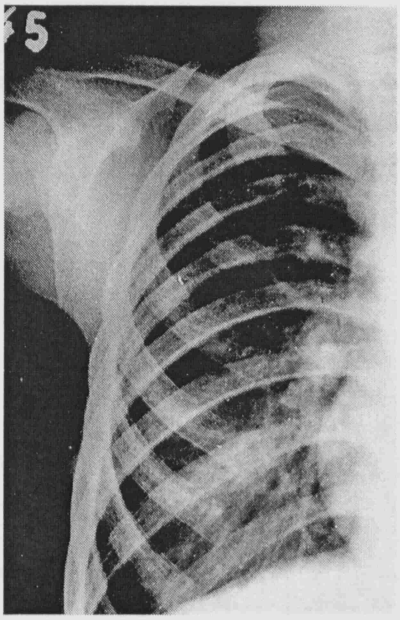


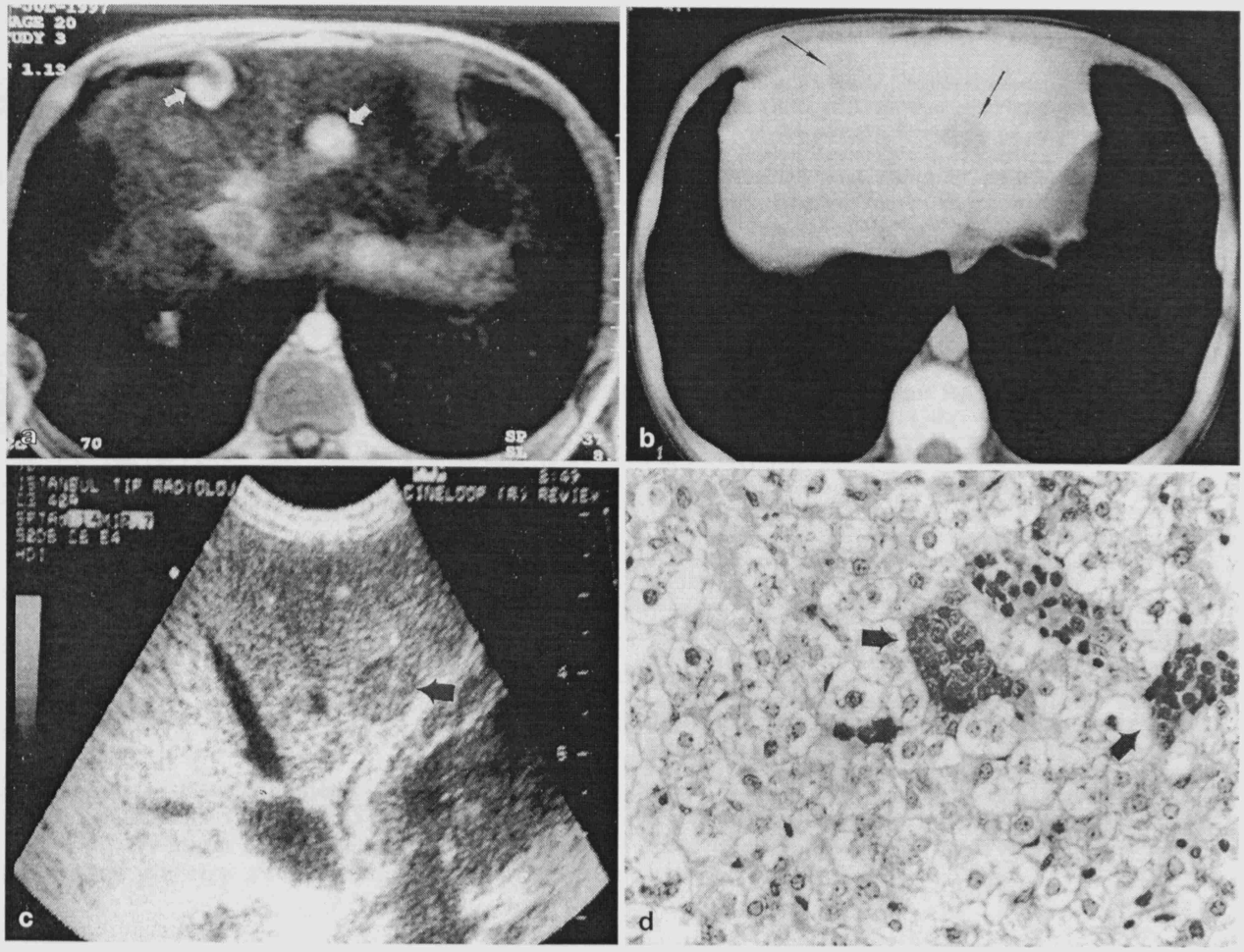
Fig. 10. Rib-in-rib appearance of a patient with thalassemia major

portant alteration in blood cell population. In thalassemia, posterior mediastinal paravertebral masses or presacral masses represent sites of ExmH resulting from extraosseous extension of medullary tissue. Also ExmH can arise from pluripotential stem cells distributed throughout the body, and involvement of the abdominal viscera, including liver, spleen, kidneys, adrenal glands, and breast, may occur (Fig. 11) [9].

Accumulation of hemolysis products

Increased hemolysis leads to accumulation of breakdown products of heme component of hemoglobin, par-

▼ **Fig. 11a–d.** A 16-year-old patient with thalassemia intermedia. **a** T1-weighted gradient-echo (TR/TE = 140/6 ms) axial images showing hyperintense well-demarcated lesions with hypointense rim in left lobe of the liver *(arrows)*. Note the diffuse hypointensity of the liver parenchyma due to iron deposition. **b** Unenhanced CT scan showing hypodense, well-circumscribed lesions in the left lobe of the liver *(arrows)*. **c** Sonographic image demonstrating an iso-hypoechoic lesion in the left lobe of the liver *(arrow)*. **d** Pathological examination of the specimen obtained from the lesion located in the left lobe of the liver shows maturating erythroid cell colonies *(arrows)* reflecting ExmH areas



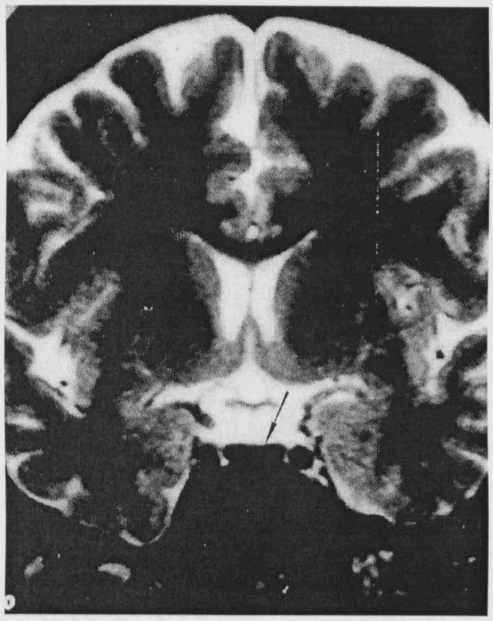


Fig. 12. A 17-year-old patient with thalassemia intermedia. T2-weighted TSE (TR/TE = 5000/119 ms, ETL = 6) coronal image demonstrating the diffuse hypointensity of the pituitary gland related to iron deposition *(arrow)*

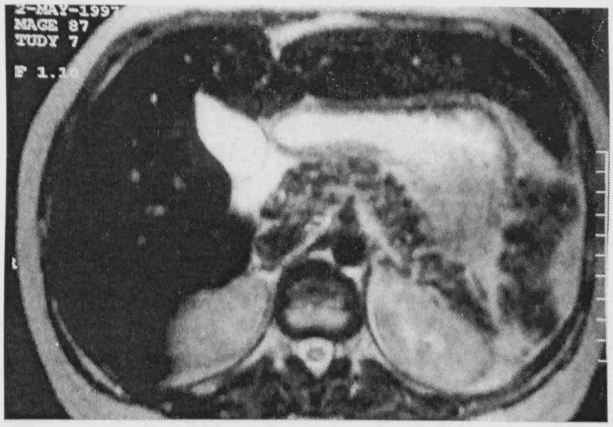


Fig. 13. A 20-year-old patient with thalassemia intermedia. T2-weighted TSE (5000/119 ms) axial image showing marked signal loss in liver and pancreas parenchyma reflecting iron deposition

ticularly bilirubin and iron. Gallbladder and bile duct diseases, especially bilirubin gallstones, are frequently seen in thalassemia cases due to increased hemolysis [10].

Hemosiderosis

Hemosiderosis is the accumulation of excess iron within the reticuloendothelial system (RES) as a consequence of repeated transfusions in thalassemias. Liver, spleen, pancreas, and pituitary gland are among the tissues that are mostly affected (Fig. 12). Magnetic resonance imaging is helpful in delineating the distribution of increased iron status in the body. As severity increases, the marrow signal intensity decreases accompanied by hypointensity of hepatic and splenic parenchyma reflecting the deposition of iron diffusely within the RES. As a consequence, MRI is an accurate modality for monitoring iron deposition in thalassemic patients [11]. Magnetic resonance imaging can be used for assessing iron overload and is believed to contribute to improving the management of thalassemia major [12]. Iron preferentially accumulates in pancreas in patients with splenectomy (Fig. 13).

Conclusion

Thalassemia is an inherited multisystemic disorder with skeletal and non-skeletal manifestations. Plain-film radiography is generally adequate in defining the routine osseous abnormalities of thalassemia. The CT and MRI techniques can document the abnormal deposition of iron, ExmH, and bone marrow changes.

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