Osteogenesis imperfecta type II: postmortem histological diagnosis on curettage material

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Abstract

Introduction

Osteogenesis imperfecta type II is one of the more common lethal skeletal dysplasias with prenatal onset. The prenatal ultrasound scan may suggest the presence of severe short limb skeletal dysplasias and can accurately predict lethality, but the final diagnosis, typing and subtyping of the specific genetic skeletal disorder are mainly based on the postmortem radiography. Histopathology of the bone and cartilage can be contributory in various skeletal dysplasias, and, in the case of osteogenesis imperfecta can be diagnostic. We describe a case of osteogenesis imperfecta type II diagnosed in a 14-week gestation fetus on the basis of the typical histopathological findings on curettage material. This report highlights the utility of histological diagnosis in certain skeletal dysplasias, even in the absence of reliable postmortem radiographic control, as is the case with curettage material in early termination of pregnancy. In addition, we document the presence of limb and rib fractures as early as the 14th week of gestation, and confirm that osteogenesis imperfecta type II can present in the first-trimester ultrasound scan with increased nuchal translucency, ventriculomegaly and generalised oedema, manifestations that are regarded nontypical for the full-blown disease.

Case report

A 35-year-old G2P1 Caucasian woman had her first-trimester ultrasound examination. The histological picture was typical of osteogenesis imperfecta type II/III. The combination of severe distortion of the limb bones with rib and limb fractures, in association with the above histopathology, permitted the diagnosis of osteogenesis imperfecta type II. The parents were referred for genetic counselling and molecular confirmation of COL1A1 or COL1A2 mutations.

Conclusion

This report underscores the utility of histological diagnosis in certain skeletal dysplasias, even in the absence of reliable postmortem radiographic control, as is the case with curettage material in early termination of pregnancy.

Introduction

Osteogenesis imperfecta (OI) is a genetic skeletal disorder characterised by decreased bone density and susceptibility to bone fractures, due to a genetic defect of mesoderm. Severity of the disease ranges from subtle to severe congenital and perinatally lethal types. Since the milestone of 'Sillence classification' into four types1, OI classification has now been expanded to seven types, accepted by most experts in the field2. The congenital forms comprise types II and III, while type II represents one of the more common lethal skeletal dysplasias that manifest prenatally and are therefore seen in the postmortem examination of the foetus2–5. In the past five years, it has become clear that OI comprises a group of heterogeneous disorders, with an estimated 90% of cases due to a causative dominant variant in the COL1A1 or COL1A2 genes, and with the remaining 10% due to causative recessive variants in various genes known so far, or in other currently unknown genes6.

OI can be prenatally suspected at the second trimester of gestation, usually during the routine morphology scan. Prenatal ultrasound may detect rhizomelic shortening and bowing of long bones, hypoechogenicity of the skull and fractures. However, the accurate diagnosis and classification to subtypes is based on the postmortem radiography. Histology of the bone and cartilage is also typical and indistinguishable in OI types II and III. To date, it is not possible to discriminate the dominant from the recessive types based on radiography and histology6,7.

In this report, we describe the postmortem diagnosis of OI type II at 14 weeks of gestation, based on the histological examination of curettage material. Early ultrasound signs are described and discussed.

Case report

A 35-year-old G2P1 Caucasian woman had her first-trimester ultrasound examination. Her husband was 41 years old. She and her husband were nonconsanguineous, and there was no family history of congenital malformations. She had a body weight of 89 kg and a body height of 162 cm. Two years before, the mother had delivered a healthy male baby with a body weight of 4400 g without any skeletal dysplasia.

Prenatal ultrasound at 13 weeks and five days of gestation revealed an increased nuchal translucency thickness of 4.0 mm, incipient generalised

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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oedema, ventriculomegaly of the brain and severely hypoplastic upper and lower limbs with mesomelic bowing. The pregnancy was terminated and the abortion material was sent for pathological examination.

On external examination of the received curettage material, only parts of the upper and lower limbs could be retrieved and appeared hypoplastic, while the skull and the thorax were deformed by the curettage procedure. The right foot and hand length were 10 mm and 8 mm, respectively, corresponding to 12 weeks of gestation. Attempted X-rays of the limbs and remnants of the trunk (not shown) showed hypoplastic humeri and femora, a severely hypoplastic radius and a bent tibia. Only the outer cortex was radiographically depicted in the severely shortened bones, while the metaphyses appeared empty. The vertebral pedicles were apparent, whereas the vertebral bodies were radiolucent, as expected at 14 weeks of gestation. The ribs and pelvis could not be radiologically assessed.

Histopathological examination of the bones (Figure 1) showed sparse and narrow metaphyseal trabeculae consisting of calcified cartilage matrix. Subperiosteal enchondrous ossification was active with very increased cellularity. Diaphyseal fractures with metaplastic cartilage were depicted in the limb bones and the ribs (Figure 2). The growth plate appeared normal for age with regular metaphyseal borders (A: haematoxylin–eosin × 50). (B) The metaphyseal trabeculae are cellular and consist of calcified cartilage matrix (B,C: hematoxylin–eosin × 200).

The combination of severe distortion of the limb bones with rib and limb fractures, in association with the above histopathology, permitted the diagnosis of OI type II.

The parents were referred for genetic counselling and molecular confirmation of COL1A1 or COL1A2 mutations.

Figure 1: Cartilage and bone histopathology in early osteogenesis imperfecta type II: (A) section from the lower limb shows sparse bony spicules in the metaphysis and diaphysis and fractured areas with distortion of the shaft, haemorrhage and formation of metaplastic cartilage (detail in C). The growth plate (upper part) appears normal for age with regular metaphyseal borders (A: haematoxylin–eosin × 50). (B) The metaphyseal trabeculae are cellular and consist of calcified cartilage matrix (B,C: hematoxylin–eosin × 200).

Figure 2: Bone distortion and fractures in sections from the upper limb (A) and a rib (B); the histological pattern is similar as in the lower limbs (hematoxylin–eosin × 50).

Discussion

During pregnancy, the most commonly defined skeletal dysplasias are OI type II, thanatophoric dysplasia and achondrogenesis type II, accounting for almost 40% of the 2000 prenatal cases reported to the International Skeletal Dysplasia Registry. Precise prenatal diagnosis of the specific skeletal dysplasias allow accurate counselling with respect to perinatal lethality, prediction of neonatal morbidity, specification of targeted molecular analysis...
and estimation of the recurrence risk in subsequent pregnancies.

The foetal skeleton is relatively well-visualised by ultrasound during the routine morphology scan so that skeletal dysplasias with prenatal onset, especially those severe disorders with pronounced shortening of long bones, are often suspected. However, given the large variety and complexity of these anomalies, antenatal diagnosis of the specific disorder is difficult. The prenatal ultrasonographic evaluation can usually predict lethality, but very often fails to identify the particular type of skeletal dysplasia, which is necessary for genetic counselling and future prenatal diagnosis. Since prenatal ultrasound accuracy in the final diagnosis of genetic skeletal disorders remains relatively low, the impact of the specific diagnosis is still dependent on the molecular genetic analysis or postmortem examination. The postmortem radiography is definitely the main diagnostic tool for the correct diagnosis and typing of foetal skeletal dysplasias. In many instances, in addition to the X-rays, the possible extraskeletal pathological findings at autopsy and the histopathological picture of bones, cartilage, and occasionally other organs, are confirming or contributory to the diagnosis.

Subsequently, the phenotypic diagnosis is ideally confirmed by molecular testing, so that the final diagnosis of a skeletal dysplasia is established.

In this report, we describe the diagnostic features of lethal OI type II established on curettage material at 14 weeks of gestation. The value of our report lies on the demonstration of the first-trimester scan were suggestive of a lethal skeletal dysplasia, but nonspecific to the final diagnosis. Increased nuchal translucency, ventriculomegaly, generalised oedema and hypoplastic long bones, reported in various combinations, have all been previously described as early ultrasound signs in foetuses with OI.

These findings, however, could also apply (and even more so) for other lethal skeletal dysplasias, such as achondrogenesis type I/II, thanatophoric dysplasia, hypophosphatasia, etc. The histological documentation of limb and rib fractures limited the differential diagnosis between OI II/III, achondrogenesis I/II and hypophosphatasia. The typical histological lesions of the metaphysis, combined with a normal appearing growth plate and no evidence of intracytoplasmic inclusions that characterise achondrogenesis, led to the diagnosis of OI. The severe distortion of the limb bones refined the diagnosis to OI type IF, one of the more common occurring lethal skeletal dysplasias with prenatal onset.

OI type II is a perinatally lethal genetic disorder caused by autosomal dominant mutations in the COL1A1 or COL1A2 genes. When the parents are phenotypically normal, the disorder is considered sporadic, attributed to de novo mutations, with occasional recurrence due to germ-line mosaicism. The parents in our case were therefore provided with a precise diagnosis, genetic counselling was feasible and targeted molecular confirmation was suggested, sparing the family from superfluous costly genetic testing.

Conclusion

This report underscores the utility of histological diagnosis in certain skeletal dysplasias, even in the absence of reliable postmortem radiographic control, as is the case with curettage material in early termination of pregnancy. In addition, we document the presence of limb and rib fractures as early as the 14th week of gestation in an affected foetus with OI type II, and confirm the previously reported observations that OI can present in the first-trimester ultrasound scan with increased nuchal translucency, ventriculomegaly and generalised oedema, manifestations that are regarded nontypical for the full-blown disease.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

Case report