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Case Report

Spontaneous resolution of severe non-immune hydrops fetalis with unknown etiology in the 32nd week of pregnancy: a case report and short review

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Summary

Non-immune hydrops fetalis (NIHF) is a symptom of other underlying complications during pregnancy, such as lymphatic dysplasia and cardiovascular, hematologic, and chromosomal disorders. The incidence of spontaneous resolution of NIHF is 5.7% and mostly occurs in cases of known etiology. Here, the authors report the case of a 29-year-old healthy primipara admitted to the hospital at 21 weeks' gestation due to pleural and peritoneal effusion, and edema of subcutaneous tissue of the fetus. Diagnostic examinations failed to reveal the etiology of NIHF. Due to an increase in hydrops, thoracentesis, and several cordocenteses with administration of albumins were performed. At 32 weeks, hydrops resolved completely with no recurrence. The baby, without any signs of hydrops, was delivered by cesarean section at 38 weeks. Diagnosing NIHF cases is difficult and requires many examinations to evaluate the etiology of the disorder, its management, and prognosis. NIHF resolving spontaneously without any consequences for child's development rarely occurs.

Key words: Non-immune hydrops fetalis; Spontaneous resolution; Intrauterine treatment; Pleural effusion.

Introduction

Non-immune hydrops fetalis (NIHF) is not considered a disease, but rather a symptom secondary to other complications during pregnancy. In the literature, it is defined in various ways. The diagnosis is made on the basis of an ultrasound examination. Some authors claim NIHF can be diagnosed in cases of generalized edema of the subcutaneous tissue of the fetus, with or without fluid collection in body cavities [1]. Others define it as generalized edema of subcutaneous fetal tissue with fluid accumulation in at least one of the body cavities [2] or fluid accumulation in at least two body cavities, or generalized edema of the subcutaneous tissue of the fetus with fluid accumulation in one of the body cavities [3] or even fluid accumulation in at least two of the fetal body cavities (of the pleural cavity, peritoneal cavity, or pericardium), and generalized skin thickening [4]. The differences in the above definitions may be due to the different intensity of symptoms [5]. In some cases, the thickening of subcutaneous tissue is easily visible while fluid accumulation in fetal body cavities is sparse, and cannot be assumed to be abnormal. In other cases, fluid accumulation in the body cavities dominates, while skin thickening is not visible.

The incidence of NIHF is estimated at different levels, as well. Sobczuk *et al.* [4] reported the incidence as one per 2,000 to 3,000 pregnancies, Heinonen *et al.* [6] one per 2,500-3,000, and Henrich *et al.* [7] one per 1,500-4,000. The data differ for many reasons. Some authors included hydrops occurrence in the course of the entire pregnancy, but some only in the first or second trimester; some included single or also multifetal pregnancies, some used cases with chromosomal defects, and others without any genetic disorders, etc. Moreover, the statistics may be incomplete because many embryos with NIHF are spontaneously lost in the first trimester of pregnancy. An additional problem is gathering a sufficiently large study population, as many reports are based on small study groups.

Case Report

A 29-year-old primipara without any diseases in her medical history, without any addictions or family disorders, was admitted to the hospital at 21 weeks' gestation due to fluid accumulation in the pleural and peritoneal cavities, as well as the subcutaneous tissue of the fetus, as revealed during a routine ultrasound examination. Prenatal tests in the first trimester were not performed. The patient denied any other complications. The ultrasound examination showed a 2-cm thick posterior placenta, 3-vessel umbilical cord, normal umbilical attachment, and a female fetus with a normal structure of internal organs. Additionally, effusions of 4 mm in the pleural cavity and 2 mm in the peritoneal cavity were observed (Figure 1), and edema of the subcutaneous tissue re-

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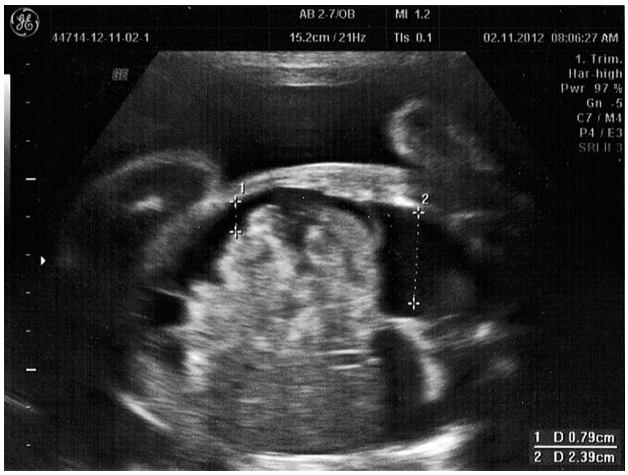

Figure 1. — The effusion in the pleural and peritoneal cavities.

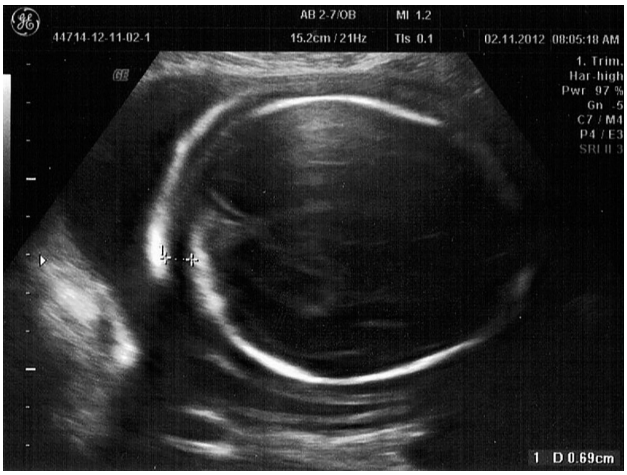

Figure 2. — The edema of the subcutaneous tissue of the fetus.

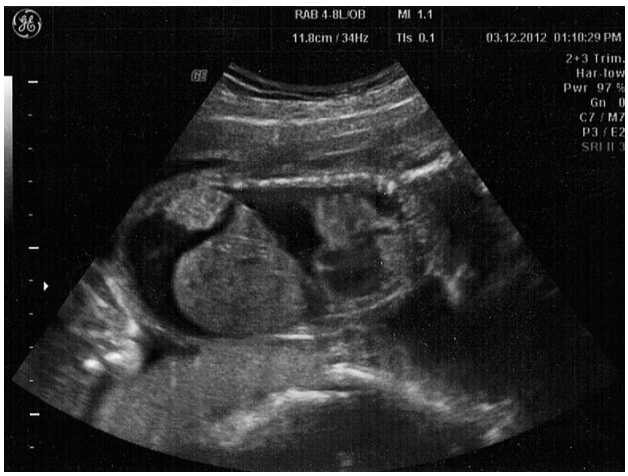

Figure 3. — An increase in fluid accumulation in the pleural and peritoneal cavities.

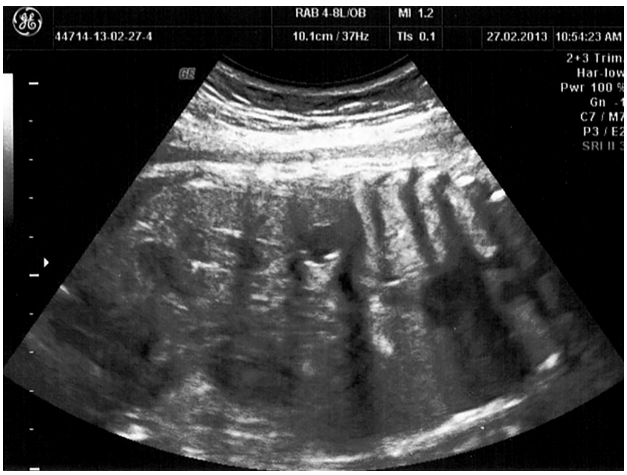

Figure 4. — Spontaneous resolution of the effusions in body cavities.

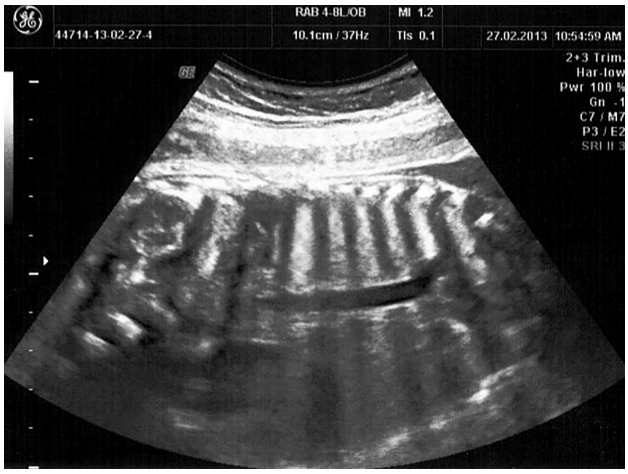

Figure 5. — No effusion in the pleural and peritoneal cavities.

sulting in a 5-mm thickness of the skin around the head of the fetus (Figure 2) was also noted. Amniotic fluid volume was normal. No heart defect or circulatory failure was found. On the basis of maternal blood analysis, immune and infection etiology of the hydrops was excluded. An amniocentesis for chromosomal analysis was performed and revealed a normal karyotype. Examinations of amniotic fluid showed no metabolic abnormalities, and also excluded an intrauterine infection of the fetus. A vaginal culture identified no infection.

As the size of the effusion increased (mainly in the pleural cavity which is showed in Figure 3), the decision was made to perform fetal thoracentesis at 22 weeks' gestation, and 18 ml of yellowish clear liquid was aspirated and tested; however, no significant cause of NIHF was found. At 23 weeks' gestation, a gradual increase in NIHF was observed, so cordocentesis was performed. Fetal blood was sampled and a direct fetal infusion of 10% solution of human albumin was administered. Laboratory data were as follows: hemoglobin 12.4 g/dl, proteins 6.3 g/dl, and albumins 3.0 g/dl. The procedure was difficult due to the place-

ment of the placenta; however, after laying the pregnant woman in the lateral position, the position of the fetus allowed for good access to the origin of the placental umbilical cord. Immediately following the procedure, a decrease of fetal hydrops was observed, but soon, a gradual increase in fluid accumulation appeared. Cordocentesis with an infusion of human albumins was repeated at 25, 27, and 30 weeks' gestation. Fetal blood test results were similar to the first examinations. Cardiotocography showed slightly decreased variability with normal fetal baseline heart rate. Doppler flows in fetal arterial and venosus vessels were normal.

At 31 weeks' gestation, a sudden decrease of subcutaneous tissue thickness and effusion in body cavities was noticed (Figure 4). By 32 weeks, only a residual trace of fluid and a small edema of subcutaneous tissue on the head of the fetus were observed. During subsequent gestational weeks, ultrasound examinations did not show any symptoms of NIHF (Figure 5). Both cardiotocograms and Doppler flows in fetal vessels were normal. The pregnancy continued until 38 weeks under strict monitoring of fetal wellbeing.

The delivery by cesarean section was performed at 38 weeks' gestation due to the presence of threatening signs on the cardiotocography. A live, term, 3,070 g and a 51-cm female newborn was delivered with Apgar score of 9. The pH of the umbilical cord blood after delivery was 7.32. Histopathological assessment of the placenta showed only three small foci of pale infarctions. The results of many examinations of the infant appeared to be normal and did not allow for identifying either the cause of NIHF or the mechanism of its unexpected resolution. The child is three-years-old now and her development is normal.

Discussion

Clinical classification of hydrops in terms of etiology encompasses immune and NIHF. Immune hydrops is mostly the result of an Rh blood group incompatibility between the mother and the fetus and was first described by Potter in 1943 [8]. Classification of non-immune hydrops was presented by Santolaya *et al.* in 1992 [9]. NIHF can be caused by many factors and as a result, its diagnosis is complex and difficult [4]. Bellini *et al.* [10], on the basis of systematic review and his own studies, divided the causes of NIHF into 14 groups, and determined the incidence of complications during pregnancy which lead to NIHF development. His study includes 5,000 cases. The NIHF classification encompasses the following 14 etiologies: cardiovascular (20.1%), lymphatic dysplasia (15%), hematologic (9.3%), chromosomal (9%), infections (7%), syndromic (5.5%), twin-to-twin transfusion syndrome and placental (4.1%), thoracic (2.3%), inborn errors of metabolism (1.3%), gastrointestinal (1.3%), urinary tract malformations (0.9%), extra thoracic tumors (0.7%), miscellaneous (3.6%), and idiopathic (19.8%). Despite continuous advances in perinatal care and improvement of diagnostic methods, between 13.2-40.0% of the causes of NIHF still remain unknown and are classified as idiopathic [4, 6, 9, 11]. Determining the cause of NIHF is extremely important, because it would help to manage it, give rational indications for intrauterine treatment, and supply important information related to prognosis [5]. Bellini *et al.* [12] and Moreno *et al.* [11] proposed a diagnostic flow chart for NIHF cases. It is estimated that, at present, 90.5% cases of NIHF can be diagnosed during prenatal tests [11, 13]. This complication occurs more frequently in female (58.5%) than in male fetuses (41.5%) [11]. The overall mortality rate of fetuses and newborns with NIHF ranges from 57.5% to 87.9% [5, 6, 9, 11, 14], including a prenatal mortality rate of 55.0% to 56.6% [11, 13].

In the literature, reports on the spontaneous resolution of severe NIHF during pregnancy are rare. They are even less frequent in idiopathic hydrops [15, 16]. According to Moreno *et al.* [11] the incidence of spontaneous resolution of NIHF during pregnancy is 5.7%. Most cases are related to a specific cause of NIHF, including aneuploidy [17], lymphatic disorders [17, 18], parvovirus B19 infection [18-21], or hematologic etiology [22]. Spontaneous and complete resolution of severe NIHF of unknown etiology during pregnancy is described only in single case reports. In the present authors' material, which includes 47 pregnant women with NIHF (data not published), they observed only one case of a pregnancy course like this. Henrich *et al.* [7] described a case of spontaneous resolution of NIHF diagnosed at 19 weeks' gestation. Edema affected the subcutaneous tissue of the fetus, and effusion was detected in the peritoneal and pleural cavities. Hydrops resolved after six weeks without any treatment. The pregnancy continued until 41 weeks' gestation. After labor induction, vaginal delivery with vacuum extraction was performed. The newborn did not present any features of hydrops. The only disorder revealed during the newborn period was uncritical atrial septal defect type II. The general condition during infancy period was good. In the present report, the time between diagnosis of NIHF and its resolution was 12 weeks. Additionally, due to the severity of the symptoms of NIHF, the case described in this paper required administration of intrauterine interventions.

In the case of NIHF reported here, hydrops affected the subcutaneous tissue of the fetus and both the pleural and peritoneal cavities. The overall pathophysiology and etiology of NIHF were explained by Bellini and Hennekam [23]. Reports from the literature describe various onsets, severity, and sequences of occurrence of excessive fluid accumulation in the extravascular compartments of the fetus. The described case of NIHF was diagnosed at 21 weeks' gestation. In the present study material (data not published), the median onset time was 21 weeks' gestation, similar to the results of Moreno *et al.* [11] and Mascaretti *et al.* [13]. Different outcomes were presented by Fukushima *et al.* [5]. In their study group of 214 NIHF cases, hydrops appeared before 22 weeks' gestation in 29% of fetuses, while in the remaining pregnancies the onset of symptoms began between 22 and 30 weeks of gestation. Similar outcomes were reported by Swain *et al.* [15]. The general principle states that the sooner hydrops of the fetus appears, the worse the prognosis is for its survival [4]; however, the most impor-

tant prognostic and decisive factor is the etiology of the disease.

In most cases of NIHF, fluid accumulation is evenly distributed, but fluid may also be present only in some areas of the body of the fetus, for example, only in the pleura [24]. In cases of severe NIHF with progressively increasing effusions, intrauterine interventions such as cordocentesis, administration of human albumins, intrauterine blood transfusion, decompression of body cavities, placing of shunts into body cavities (e.g. pleura), digitalization, and/or amnioreduction in polyhydramnion [4, 5] may be required. In the case reported here, amniocentesis was performed in order to assess the fetal karyotype and diagnose possible infections or metabolic disorders. To perform this required decompressing and analyzing fluid sampled from pleural cavities, as well as conducting repeated cordocentesis with intravascular human albumin infusions. Usually, NIHF is associated with protein deficiency in the serum of the fetus; therefore, protein supplementation is necessary as symptomatic treatment in severe hydrops. In the present case, such treatment resulted in a decrease in hydrops and a prolongation of the pregnancy.

Conclusions

Diagnosing NIHF cases is difficult and requires many examinations to evaluate the etiology of the disorder, its management, and its prognosis. It rarely resolves spontaneously without any consequences for child's development.

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