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Case Report

An Intrauterine Case of Explosive Growth of Neurofibromatosis during Pregnancy with Fetal Death in Mid-Pregnancy: A Case Report

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Keywords
Eruptive neurofibromas · Neurofibromas · Neurofibromatosis type 1 · Pregnancy

Abstract
Introduction: Neurofibromatosis type 1 (NF1) is one of the most prevalent autosomal dominant inherited diseases, with an incidence rate of 1/3,000. The hallmark clinical features of NF1 include coffee milk spots, multiple neurofibromas, and freckles in the armpit or groin. Numerous studies have indicated a higher incidence of pregnancy-related complications in patients with NF1, including fetal growth restriction and preeclampsia. ***Case Presentation:*** This case study describes a pregnant woman with NF1 who unfortunately experienced intrauterine fetal death during her second trimester and developed preeclampsia and HELLP syndrome. ***Conclusion:*** This case highlights the need for close monitoring and management of patients with NF1 during pregnancy and the critical role of multidisciplinary collaboration and follow-up of MDT.

Introduction

Neurofibromatosis type 1 (NF1) is one of the most prevalent autosomal dominant inherited diseases, with an incidence rate of 1/3,000 [1]. The hallmark clinical features of NF1 include coffee milk spots, multiple neurofibromas, and freckles in the armpit or groin [2]. Numerous studies have indicated a higher incidence of pregnancy-related complications in

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patients with NF1, including fetal growth restriction (FGR) and preeclampsia [3]. Based on the results of the examination, the pregnant woman was diagnosed with NF1, an autosomal dominant genetic disorder, which causes multisystem damage due to abnormal development of neural ridge cells as a result of genetic defects. This condition can affect multiple systems, including the skin, peripheral or central nervous system, bone, vascularization system, and endocrine system.

Case Presentation

General information of the patient is as follows: female, 31 years old, 27+5 days pregnant, admitted to the hospital on April 10, 2023, due to "FGR, abnormal fetal cord blood flow, and preeclampsia." History of present disease was that the patient reported a diagnosis of cutaneous neurofibromatosis at a foreign hospital more than 10 years ago, following the discovery of scattered brown plaques on her body. Aside from the skin plaques, she experienced no discomfort and did not receive any special treatment. The patient had not undergone regular birth examinations. She self-reported a significant increase in the number of brown plaques on her body during pregnancy, compared to prepregnancy levels (Fig. 1a, b). On March 4, 2023, during a routine birth examination, the following findings were observed on fetal color ultrasound: (1) a single live fetus (clinical gestational age 22.3 w, ultrasonic gestational age 20.6 w, amniotic fluid depth 4.6 cm, S/D 4.48, estimated fetal weight 391 g, U-shaped indentation visible on the fetal neck); (2) placental location – the placenta was situated on the left lateral wall of the fundal uterus, measuring approximately 10.0 × 4.5 cm, with the lower margin 6.4 cm from the internal cervix. Chromosome microarray screening of the amniotic fluid on April 7, 2023, indicated no obvious abnormalities. At 27+5 weeks of pregnancy, the patient presented to our hospital for prenatal examination. Fetal B-ultrasound findings indicated "single live fetus; fetal presentation: head, double parietal diameter 6.1 cm, fetal estimated weight 761 g, clinical gestational age 27.5 w, ultrasonic gestational age equivalent to 24.6 w; high PI value of the middle cerebral artery, severe anemia, reversed diastolic blood flow in the umbilical artery; the heart is slightly enlarged, and there is a small amount of fluid in the pericardial cavity." Previous history was that there was no genetic testing for cutaneous neurofibromatosis in her grandmother, father, and elder brother. This was a natural pregnancy, G3P0, with two previous biochemical miscarriages. Physical examination on admission reported mild facial swelling, freckles on the face, scattered coffee pigment spots in various shapes throughout the body, accompanied by large and small cystic nodules of mung beans, clear breathing sound in both lungs, no dry and wet rales, abdominal swelling, no tenderness and bouncy pain, no edema in both lower limbs.

Physical examination reported the following: blood pressure – 151/111 mm Hg, mild edema of lower limbs. Auxiliary test was done on April 11, 2023. Urine routine (urine analysis) indicated protein 1+. A bulging mass approximately 5 cm × 3 cm × 2 cm in size was noted at the root of the left lingual margin. The mass was soft, with clear boundaries, no redness, swelling, tenderness, and moderate mobility. Neurofibroma was considered.

Fundus examination revealed bilateral papilledema and iris hamartomas, consistent with fundus changes in neurofibromatosis. Physical examination reported intraocular pressure 13 mm Hg in the right eye, 14 mm Hg in the left eye, iris with scattered yellow nodules in both eyes. Fundus photography showed scattered yellow mass lesions on the retinas of both eyes, each approximately 1 PD in diameter, with involvement of the macula in the right eye.

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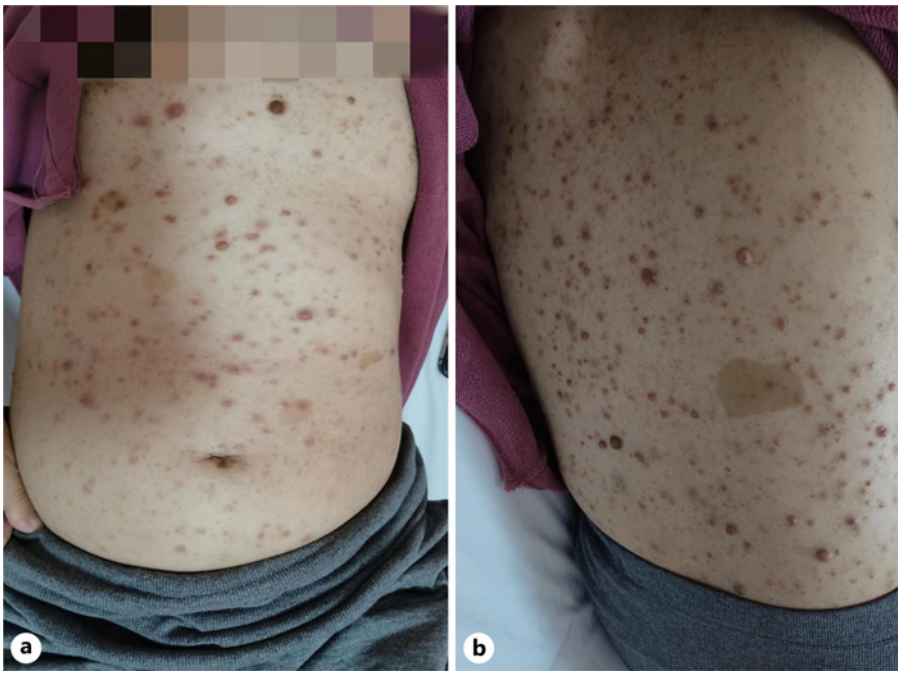

Fig. 1. Some representative image of this neurofibroma in this case. **a** Coffee-colored plaques and multiple nodules in the chest and abdomen during the second and third trimester. **b** Brown plaques and multiple nodules on the back after the second and third trimesters.

Perimetry examination showed defects in the peripheral visual field of both eyes. (1) Hamartoma of the iris and (2) fundus changes in neurofibromatosis were considered. Cerebral CT scan showed multiple nodular changes.

Head MRI shows brain plain scan + diffusion imaging. Examination results were (1) abnormal signal nodules in the midbrain, considering brain infiltration by neurofibromatosis; clinical correlation recommended; (2) softening lesion with gliosis at the right ventricle frontal angle (Fig. 2a). Neck MRI shows (1) mixed signal foci on the left anterior wall of the oropharynx and nasopharynx, compressed near the pharyngeal cavity; (2) multiple abnormal signal foci on the anterior aspects of both sides of the neck; multiple subcutaneous nodules in the posterior neck and thoracic back on both sides with neurofibroma are suspected based on medical history (Fig. 2b). Lumbar plain scan (MRI) shows multiple nodules can be found subcutaneous in the back of the chest, back of the waist, and sacrococcygeal tail, accompanied by subcutaneous soft tissue edema, and neurofibroma may be possible (no spinal canal occupying was found) (Fig. 2c). In the full abdominal CT plain scan + enhancement, the examination results were as follows: (1) left adrenal junction nodule, adenoma; (2) multiple subcutaneous nodules in the lower back were considered neurofibroma based on medical history (Fig. 2d).

For the treatment, a multidisciplinary consultation was performed on April 14, 2023. The patient had not undergone genetic testing or prenatal diagnosis during pregnancy and developed complications related to NF1, including preeclampsia, FGR, and an increased risk of preterm birth. During labor, the patient was at risk for severe complications, including cerebral hemorrhage, cerebral edema, acute liver and kidney failure, HELLP syndrome, fundus hemorrhage, and retinal detachment. Given the complex and serious nature of the patient's condition, upon hospital admission, treatments to promote fetal lung maturation and provide magnesium sulfate for brain protection were initiated. Symptomatic support included

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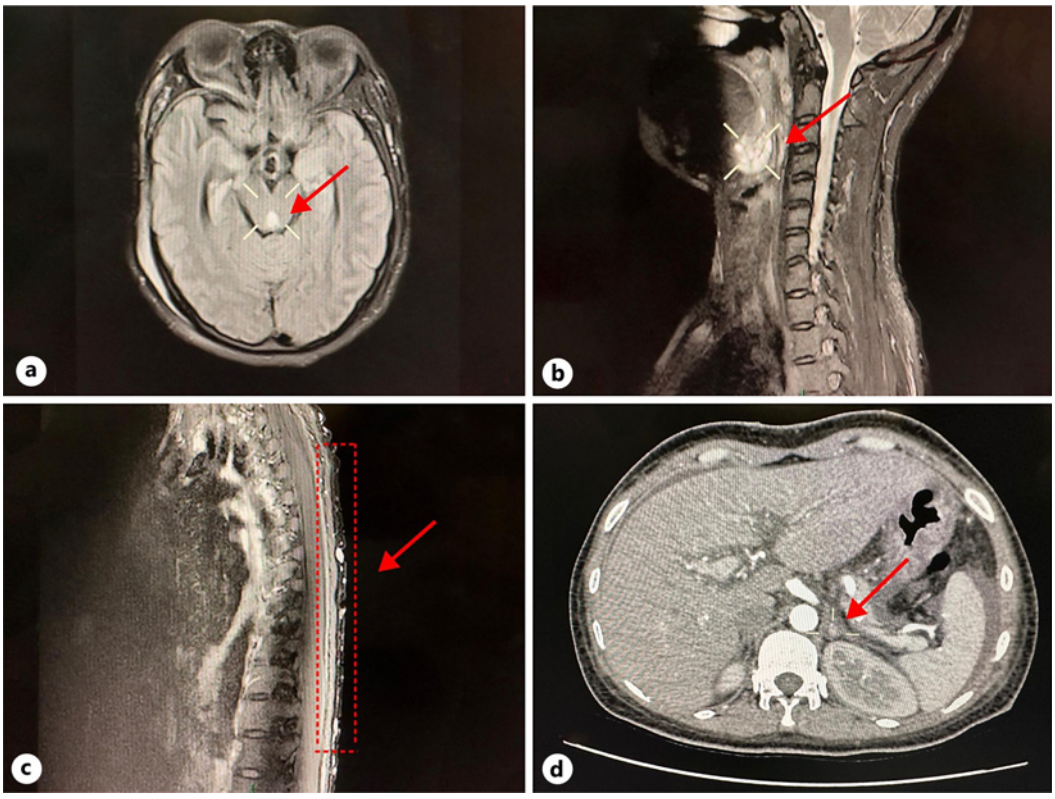

Fig. 2. Some representative imaging features of neurofibroma in this case. **a** Head MRI: abnormal signal nodules in the midbrain, considering neurofibromatosis brain infiltration. **b** Neck MRI: mixed signal foci in the left anterior wall of oropharynx and nasal cavity, narrowed by compression near the pharyngeal cavity. **c** Multiple subcutaneous nodules in the lower back and sacrococcygeal region, with possible neurofibroma. **d** Full abdominal CT: left adrenal junction nodule, adenoma.

nifedipine, labetalol for antihypertensive therapy, and magnesium sulfate for spasmolytic treatment. On April 19, 2023, the patient's blood pressure was 173/101 mm Hg, prompting the immediate administration of 100 mg of oral labetalol. After 30 min of rest, the blood pressure was rechecked at 170/98 mm Hg. ECG monitoring was started, and intravenous antihypertensive treatment was rapidly administered. The woman complained of tightness and stiffness in the lower abdomen and a sensation of falling. Urgent urine routine indicated protein 2+ ↑, ketone body negative, white blood cell (esterase) 1+ ↑, suggesting potential kidney function impairment. The patient exhibited systemic edema, and blood pressure control remained inadequate. B-ultrasonography showed stagnation in fetal weight gain, with absent umbilical artery blood flow during the diastolic period. Three stages of fetal heart monitoring showed no fetal heart activity. After thoroughly explaining the seriousness of the condition and the possible risks to the patient and family, a decision was made to proceed with the termination of pregnancy. On the morning of April 22, rivanol amniocentesis was performed, and later that evening, the patient was transferred to the delivery room due to regular abdominal pain. In the early morning of April 23, the patient's blood pressure reached 173/110 mm Hg, and her heart rate was 89 bpm. She continued to experience intermittent abdominal distension and pain. After consultation, the adult ICU doctor was asked to give 0.9% sodium chloride injection 40 mL + urapidil hydrochloride injection 50 mg intravenous pump according to the doctor's advice. The pregnant woman gave birth to a baby girl at 05:00 on April 23, 2023. It weighed 805 g and was 39.0 cm long. No umbilical cord was wrapped.

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Table 1. A detail timeline of the case

Date	Event	Management
March 4, 2023	Routine prenatal examination at 22 weeks: fetal ultrasound revealed growth restriction (sonographic gestational age 20.6 weeks), localized placenta, and elevated umbilical artery S/D ratio (4.48)	Outpatient recommendation: nutritional optimization; no regular follow-up or further intervention
April 7, 2023	Amniotic fluid chromosomal microarray analysis: no significant abnormalities detected	No NF1 genetic testing performed; fetal genetic risk not clarified
April 10, 2023	Hospital admission at 27+5 weeks for "FGR, abnormal umbilical blood flow, and preeclampsia"	Admission findings: BP 151/111 mm Hg, proteinuria 1+; initiated magnesium sulfate and labetalol (antihypertensive therapy)
April 14, 2023	Multidisciplinary team (MDT) consultation: confirmed NF1 diagnosis, evaluated preeclampsia, and placental circulatory insufficiency	Administered dexamethasone (fetal lung maturation) and adjusted antihypertensive regimen (nifedipine + labetalol)
April 19, 2023	Uncontrolled hypertension (BP 173/101 mm Hg) and absent fetal cardiac activity	Initiated labor induction protocol; intravenous urapidil infusion for blood pressure control
April 22, 2023	Rivanol amniocentesis for labor induction; transferred to delivery room	Monitored uterine contractions and blood pressure; amniotic fluid grade III meconium staining
April 23, 2023	Vaginal delivery of a stillborn female infant (805 g); postpartum diagnosis of HELLP syndrome	Hepatoprotection (glutathione), renal protection (hydration), platelet transfusion; monitored D-dimer and hepatic enzyme levels
April 25, 2023	Postpartum day 2: platelet count 30 × 10^9/L, significant elevation of hepatic enzymes	Continued hepatoprotective therapy; monitored coagulation profile and renal function
April 27, 2023	Discharge: stable blood pressure, declining hepatic enzymes (ALT 84 U/L, AST 63 U/L), platelet recovery	Discharge recommendations: regular multidisciplinary follow-up, tumor surveillance, and metabolic monitoring

FGR, fetal growth restriction.

The amniotic fluid was classified as grade III, and the placenta was delivered naturally. The fetal membrane was found to be incomplete, and a uterine clearance operation was performed. The perineum sustained a grade I laceration, with a total blood loss of 200 mL during delivery.

Treatment results on April 25 were as follows: the second day after delivery, the patient reported abdominal discomfort, and generalized edema remained unresolved. Laboratory tests revealed the following: blood routine examination + hypersensitive CRP – hypersensitive C-reactive protein 31.28 mg/L ↑, hemoglobin 100 g/L ↓, total platelet 30 × 10^9/L ↓, plasma D-dimer 13.58 μg/mL ↑; liver and kidney function – alanine aminotransferase 127 U/L ↑, aspartate aminotransferase 242 U/L ↑, lactate dehydrogenase 934 U/L ↑, α-hydroxybutyrate dehydrogenase 569.00 U/L ↑, creatine kinase 251 U/L ↑, creatine kinase isoenzyme 29.3 U/L ↑ (platelets decreased significantly, liver enzymes increased, lactate dehydrogenase increased, D-dimer increased). Additional diagnosis reported HELLP syndrome. Symptomatic treatment of liver and kidney protection was carried out, and close observations were made. On April 27,

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the patient's abdominal discomfort had resolved, and subsequent laboratory results showed improvement in the previously elevated markers: liver and kidney function – alanine aminotransferase 84 U/L ↑, aspartate aminotransferase 63 U/L ↑, albumin 27.4 g/L ↓, lactate dehydrogenase 323 U/L ↑. The patient's body temperature was normal, urine and bowel movements were regular, and lochia volume was less than menstrual volume. Blood pressure remained well controlled, and HELLP syndrome gradually improved. Given these clinical improvements, the patient was discharged.

Discussion

In this case, the patient was diagnosed with NF1 based on the presence of multiple body, coffee, and clinical manifestations of the nerve fibroma involving extensive areas of the body. Notably, the patient exhibited a marked increase in cutaneous neurofibromatosis during pregnancy – a relatively uncommon presentation among patients with NF1. Existing studies have suggested that cutaneous and subcutaneous neurofibromas in NF1 patients may increase in volume during pregnancy, potentially due to hormone-dependent growth mechanisms. However, cutaneous neurofibromas exhibit a significant increase in growth over time in both pregnant and nonpregnant patients, with NF1-related clinical symptoms not significantly worsening during pregnancy [4]. Kitano et al. [5] demonstrated that Schwann cell proliferation in neurofibromas, induced by epidermal growth factor, transforming growth factor alpha, and fibroblast growth factor, occurs at relatively low levels. This phenomenon may contribute to the observed increase in both the number and size of neurofibromas in pregnant patients.

Sarcoma is a rare malignant tumor that originates in the interstitial tissue. For advanced or metastatic sarcomas, traditional treatments such as surgery, radiation, and chemotherapy exhibit limited efficacy. Consequently, the identification of predictive biomarkers for therapeutic response has become a focal point of contemporary research. Mutations in genes such as *TP53*, *RB1*, *ATRX*, and *PTEN* have been implicated in the initiation and progression of these tumors [6, 7]. Immunotherapy has made significant strides in cancer treatment; however, it also introduces new challenges. Immune checkpoint inhibitors combat tumors by activating the immune system but can also provoke adverse effects, including hearing loss, peripheral neuropathy, and headaches [8, 9]. Additionally, prognostic tools like the RMH score provide a quantitative means of assessing a patient's health status [10]. These tools not only aid in predicting treatment outcomes but may also contribute to the development of a prediction system for NF1 pregnancy complications.

In addition, patients with NF1 are at an increased risk for obstetric complications, including pregnancy-induced hypertension, preeclampsia, FGR, and preterm birth [11]. Cecchi et al. [12] reported a case of an NF1 pregnant woman who died due to acute pulmonary edema and supraventricular arrhythmia during a cesarean section. Postoperative autopsy revealed the presence of pheochromocytoma, which had not been screened for during the pregnancy. Despite the patient's blood pressure remaining within the normal range, pheochromocytoma could not be excluded. Additionally, the patient developed complications such as preeclampsia and FGR, followed by the onset of HELLP syndrome after delivery. HELLP syndrome, a rare and serious pregnancy complication, is characterized by hemolysis, elevated liver enzymes, and thrombocytopenia. Since admission, the patient was not compliant with treatment measures, and blood pressure control was suboptimal. It was not until the second day after delivery that the diagnosis of HELLP syndrome was made.

Conclusion

This case systemically reveals the multidimensional challenges in managing NF1 during pregnancy and highlights the core value of multidisciplinary team (MDT). As an autosomal dominant genetic disorder, NF1 causes neurofibromas to grow very quickly in pregnant women. This is strongly linked to elevated estrogen levels and placental microcirculation disorders [13]. These factors significantly increase the risks of preeclampsia, HELLP syndrome, and intrauterine fetal death. According to the international guidelines from 2023, an MDT should encompass the following disciplines: obstetrics for dynamic monitoring of tumor volume changes and placental blood flow parameters (such as umbilical artery S/D ratio); neurology for evaluating the progression of intracranial lesions such as optic pathway gliomas and plexiform neurofibromas through brain MRI; ophthalmology for screening iris hamartomas (Lisch nodules) and optic pathway gliomas; genetics for providing preconception NF1 gene testing (such as PCR + Sanger sequencing) and prenatal diagnosis [14, 15]. Establishing a stratified follow-up system is necessary due to the lifelong nature of NF1: (1) tumor monitoring – whole-body MRI at 3.0T every 6–12 months, with a focus on evaluating retroperitoneal and paraspinal plexiform neurofibromas, which carry an 8–13% risk of transforming into malignant peripheral nerve sheath tumors; (2) metabolic and coagulation function assessment – annual detection of vanillylmandelic acid and metanephrines (for pheochromocytoma screening, with an incidence of 1–5%), combined with thromboelastography and monitoring of plasma norepinephrine levels to assess hypercoagulable states; (3) skeletal and neurocognitive management – perform dual-energy X-ray absorptiometry every 2 years to assess bone density and an annual full-length spine X-ray to screen for scoliosis. For offspring, initiate genetic management in the neonatal period: a full-body skin examination (counting café-au-lait macules) within 1 month after birth, completion of NF1 gene sequencing by 6 months of age, and neurocognitive assessment at key developmental stages of 3 and 6 years old [16, 17]. A comprehensive management model incorporating "preconception genetic counseling-prenatal molecular diagnosis-postnatal MDT follow-up" can significantly reduce maternal and infant complications. This approach also provides valuable clinical evidence for the study of the tumor occurrence mechanism and targeted therapy of NF1. A detailed timeline of the case is provided in Table 1.

Statement of Ethics

This study protocol has been reviewed and approved by Biomedical Research Ethics Committee at Women and Children's Hospital of Hubei province, Approval No. IEC(DM174). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The CARE Checklist and Patient Consent have been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545803).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Each author has contributed to the following sections of the manuscript: Xiyan Ouyang, gynecologic oncology (case, epidemiology and risk factors and diagnosis, and wrote the original draft); Yanli Li, gynecologic oncology (histology, assessment of pathological response, and risk factors); Xin Li, gynecologic oncology (diagnosis and assessment of clinical response, and review of the literature); Lingna Chai, gynecologic oncology (clinical coordination of the MDT and review of the literature); Han Gao, gynecologic oncology (staging and surgery, and development of a treatment plan); and Jie Shi, gynecologic oncology (staging and surgery, and revision of the manuscript).

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary materials. Further inquiries can be directed to the corresponding author.

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