

Neurofibromatosis and HIV in a pregnant woman

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Abstract

We report on pregnant woman affected by NF1 and HIV infection. So far, both NF1 and HIV in pregnancy had never reported. During 7-year follow-up, she experienced 4 pregnancies without any complication linked to NF1. The newborns were HIV-negative. A multidisciplinary counseling could improve ante and post-partum management.

Key Clinical Message

Although pregnant neurofibromatosis or HIV patient established a high risk group, this report demonstrated that a careful planning and widespread valuations should be associated with a favorable prognosis both mother and newborn.

Background

Neurofibromatosis type 1 (NF1) or Von Recklinghausen disease is a rare autosomal dominant syndrome occurring in approximately 1:3,000 births (1). It is due to gene mutation of proximal long arm of chromosome 17 with the loss of neurofibromin protein, that is involved in activation protein for RAS (4). The mutation is sporadic in about 50% of cases. The diagnosis is performed by clinical criteria according to NIH criteria (2) or by molecular study (3). NF1 is prevalently associated with histologically benign tumors of the peripheral and central nervous system with variable clinical expressions.

The aim of this paper is to describe the complex counseling in a woman with NF1 and HIV infection diagnosed at the beginning of her first gestation. The woman had four pregnancies and delivered three babies without HIV infection, two with signs of NF1. No maternal huge transformation of neurofibromas or malignant degeneration was evident in a seven years follow-up and HIV infection remained stable.

Case report

A Caucasian 26-year-old primigravida woman was referred to our gynecologic department at 12th gestational week on 2013. She was diagnosed with NF1 when 5 months years old. Analysis of DNA-sequence has been performed when she was 11 years old with MLPA method without evidence of NF1 genetic mutations. The patient had no familial history positive for NF1 with healthy parents and one sister. She had a very low income, had a secondary upper school degree and was followed by social services due to poor social conditions. She had a history of smoke, but no alcohol or illicit drug use. Body mass index was 23. Menarche occurred at eleven years of age with normal menses. Psychological and physical development were normal. She underwent multiple surgeries to remove neurofibromas mainly located in skull bone, peritracheal tissue and

next to the clavicle. Also, a palpebral neurofibroma was removed with poor esthetic result. MRI showed a 1 cm hyperdense lesion located at TH1 that was assumed to be an asymptomatic neurofibroma.

At the admission, patient was in good health with multiple evident café-au-lait patches over the skin, extensive freckling and diffuse neurofibromas in the skin, whose single maximal dimension was no more 2.5 cm in diameter. Obstetrical examination of external genitalia was normal with numerous small neurofibromas; vagina and uterine cervix appeared normal. Uterine volume corresponded to amenorrhea, with normal soft surface, no evidence of palpable mass in vagina, fornix or recto-vaginal septum. Blood pressure was normal. She did not show peripheral pitting edema. On physical examination a slight scoliosis was evident as well as a navel scar due to piercing. Heart and lung examination did not show anomalies and echocardiograph and abdominal ultrasound appeared normal. Patient refused ophthalmologic evaluation.

Fetal ultrasound showed a singleton fetus whose development was correspondent to amenorrhea (12th week). During genetic counseling the patient and her partner refused screening for fetal aneuploidies and prenatal diagnosis of NF1. A HIV-infection with low viral load (200 copies/ml) and normal CD4+ cells count (568/mm³ CD4+; CD4/CD8>1) was discovered during pregnancy evaluation at her first check-up at 12-week gestational age. Western-Blot confirmed HIV infection, but viral genotype was not performed due to the low viral load. She was considered a HIV-elite controller and closely monitored by multidisciplinary medical team that included an expert in infectious disease. Moreover she denied risk behavior, except for a piercing performed one year before in an unsafe environment with a non-sterile needle.

A multidisciplinary team made by obstetric, infectious disease (ID) specialist, anesthesiologists and neonatologist discussed with the patient the possible effects of pregnancy on the disease and possible complications linked to NF1 and also risk for an HIV positive status for the fetus.

Since 19th week of pregnancy she was treated with Emtricitabine 200 mg/Tenofovir 245 mg a day (Truvada), Ritonavir 100 mg/day (Novir) and Atazanavir 300 mg/day (Reyataz). PCR-test showed absence of HIV-RNA after one month of therapy and 496/mm³ CD4+ lymphocytes. She had no side effects due to antiretroviral therapy. The risk of low or no fetal infection during pregnancy was discussed with the couple. VDRL, TPHA, HCV, CMV, hepatitis A and B antibodies were negative. Pap test was normal and molecular test was negative for HPV infection. Vaginal culture was positive for mycoplasma infection that was successfully treated. Partner was negative for HIV and other common infection disease (HCV, hepatitis A and B, TPHA, VDRL, CMV). Doppler assessment of uterine artery was normal.

During second trimester cutaneous neurofibromas increase in numbers and dimension but none of them became relevant or giant. She then underwent routine fetal ultrasound and echocardiography that did not show any anomaly in growth or malformation. During routine anesthetic evaluation, there was no evidence of oral neurofibroma, she had adequate cervical mobility without palpable mass, and showed Mallampati 2. Near term of pregnancy lumbar MRI was suggested in order to evaluate TH1 lesions detected some years before and possible new occult neurofibroma that may have an effect on neuraxial anesthesia, if necessary, but she refused.

She spontaneously delivered a healthy female baby at 38-week gestational age without any perineal lesion. Zidovudine was promptly administered although undetectable viral load. Neonate had normal Apgar score and pH umbilical cord; she was HIV-RNA negative at birth and treated according to standard perinatal therapy with Zidovudine for 4 weeks. Lactation was inhibited. After delivery, patient continued to assume antiretroviral therapy, but refused any contraception. In the follow-up infant showed persistent negative HIV viral load.

During following years, patient had a miscarriage, and two other pregnancies. During each pregnancy she never showed increase in viral load, that remain undetectable, moreover CD4+ count was stable through years. Third pregnancy ended in spontaneous preterm delivery at 36 weeks with a healthy baby, normal Apgar score and pH in umbilical cord. There was no perineal lesion. Lactation was inhibited and the patient refused contraception.

During the forth pregnancy, the patient showed a steadily increase in CD4+ from 658/mm³ to 900/mm³. She was admitted at 33-week of pregnancy in Emergency Department for massive uterine bleeding due to abruptio placentae and she underwent emergent caesarean section. Baby was low weight and showed low Apgar score at 1 and 5 minutes (6 and 8), but normal pH in umbilical artery. Lactation was inhibited and the patient refused again contraception.

In summary, the patient was compliant with HIV therapy without increase in viral load in the four pregnancy and she refused contraception. Moreover, even with adequate counseling she refused antenatal diagnosis for NF1 or prenatal screening for fetal aneuploidies. Babies were HIV-negative, during follow up, but two had clinical signs of NF1. Moreover neurofibromas remained stable and did not show any malignant degeneration.

Discussion

The case reported is interesting due to the unique association between NF1 and HIV infection, the complexity of genetic counseling, the possible effects of pregnancy on NF1, the possible complications of pregnancy, mode of delivery and complexity of anesthesia that needs a specialized team in a tertiary level hospital.

HIV infection has been reported only in few cases in non pregnant NF1 patients. de Castro et al (4) described a 38-year-old woman with NF1 and AIDS with peripheral T-cells lymphoma with good response to chemotherapy and Isa et al (5) a 30 years old woman with HIV infection whose disease remained stable with an adequate response to antiretroviral therapy. More recently Hiesgen and Variava (6) discussed about a 30-years-old woman with NF1 and somatostatinoma who died soon after diagnosis. Also Forte (7) described a case of a 41-year-old female patient with NF1 and uncontrolled HIV infection with simultaneously supratentorial and infratentorial pilocytic astrocytoma. At best knowledge of the Authors there is no case of NF1 pregnant woman with HIV infection described in the literature.

Prenatal genetic counseling may be complex because no phenotype-genotype correlation in NF1 patients and the rare association between NF1 and HIV. Many options are available. Preimplantation diagnosis is only possible through planned pregnancy obtained by assisted reproduction but is performed only in some centers (Scout et al 2019) (8). Villocentesis or amniocentesis may be proposed when viral load is undetectable or low, because there is no increase in the risk of fetal infection (Florida et al 2017, Eppes 2017) (9,10). Furthermore the diagnosis of NF1 has been performed by evidence of NF1 paternal mutation detected in free DNA in maternal blood (Gruber et al 2018) (11). Request of prenatal diagnosis for NF1 however seems correlated to many factor such as cultural background, educational level, previous child affected, longer follow-up, awareness on the natural history of NF1 with specific knowledges of the disease (Farhi et al 2008) (12) and many NF1 patients choose not to receive prenatal diagnosis (Terzi et al 2009 (13). Our couple refused prenatal diagnosis for NF1, because no willingness to interrupt pregnancy in an affected fetus by NF1.

Current data show that fertility in NF1 young women is not compromised, but miscarriage can occur frequently. Pregnancies have been reported in women with NF1, but concerns exist for the mother and the fetus. Stroke, acute vascular rupture, hypertension, preeclampsia, low platelet count, HELLP syndrome and eclampsia have been reported (Terry et al 2015, Leppavirta et al 2017) (14,15). Particularly hypertension due to pheochromocytoma or paragangliocytoma may change the prognosis for the mother and the fetus (Walther et al 1999) (16). Nevertheless, maternal mortality in compliant patient with NF1 is rare.

Fetal pathologies such as Intrauterine Growth Retard (IUGR), oligohydramnios, preterm delivery, sudden fetal death and emergency cesarean section have been described. Fetuses may also be affected by NF1 and may present higher incidence of malformations (Leppavirta et al 2018 (17). Our patient had two preterm deliveries, one due to abruptio placentae in the absence of hypertension and two out three child had clinical signs of NF1. Vaginal delivery wasn't contraindicated due to normal pelvic examination and undetectable viral load. However in HIV patient during vaginal delivery fetal contact with maternal blood should be minimized and there are no definitive data if operative vaginal delivery may increase the risk of fetal infection (Peters et al 2017) (18).

The association of NF1 with HIV infection warrant an experienced multidisciplinary team. Generally general anesthesia should be avoided in pregnant women, but neuraxial anesthesia in asymptomatic spinal neurofibroma may be cause of specific concern in NF1 patients, because asymptomatic neurofibromas are not rare (Dounas the al 1995 et al 1999) (19). Before neuraxial anesthesia and analgesia, may be useful a MRI of the spine to detect such tumor that may contraindicate regional anesthesia (Spiegel 2005) (20). Furthermore it should be remembered that HIV infection with undetectable or low viral load is not a contraindication to local anesthesia (Gaisen 2003, Benton et Reese 2009, Gronwald et al 2011) (21,22,23).

Finally, an unknown issue is if natural pregnancy immunomodulation may increase the risk of malignancy when associated with HIV and NF1. It is known that 4-15% of NF1 patients, affected by plexiform neurofibromas, develop malignant degeneration during their life, with a latency period of about 10-20 years. Tumors usually arise before 39 years of age (Korf et al 2000) (24). This risk is cause of concerns. More rare tumors may affect NF1 patient such as pheochromocytoma, neuroblastoma and melanoma that arise from neural crest and also Wilms tumor, malignant nodular hidradenoma, leukemia, rhabdomyosarcoma, T-cell-lymphoma. Causes of high prevalence of neoplasm in NF1 patients, both benign and malignant, are not completely known, and genetic, environmental and hormonal factors may be implicated. Actually, it is unknown the possible effect, if any, of many pregnancies in the incidence of malignant degeneration in NF1 patients, but a relevant effect of pregnancy on tumor growth is well known, because up to 80% of skin tumors increases in dimensions in pregnancy (Schmutz 2003) (25). Moreover, during pregnancy many new tumors may be diagnosed, and up to 3% of NF1 patients are diagnosed during pregnancy due to the appearance of neurofibromas (Nebesio et al 2007, Cesaretti et al 2013) (26,27).

Our patient was HIV positive but maintained low viral load and normal CD4 count throughout each pregnancy, showing no evident HIV immunosuppression so probably it did not affect significantly neurofibromas growth. However through seven year of observation no relevant transformation or malignant degeneration of neurofibromas was observed.

Conclusion

In conclusion, in recent years, pregnancy is not rare in NF1 patient because normal fertility and ameliorated quality of life, the course of pregnancy may be complicated, but maternal mortality is rare. Number and size of neurofibromas frequently increase in pregnancy especially in the second trimester. NF1 patient can plan pregnancy and deliver safely with adequate counseling, but medical team should be prepared for possible maternal and fetal complications. Our patient is unique because NF1 was associated with HIV infection, she had four pregnancies, no significant increase in neurofibroma dimensions and no malignant degeneration was evident during a seven years follow-up. The association between pregnancy and HIV seropositive in compliant patient with NF1 may have a good maternal and neonatal outcome, without evident progression of HIV disease or negative effects on NF1. National or sovranational registries may be useful to better understand the long-term effects of pregnancies on NF1 and vice-versa, also in subgroup of patients such as in the case described.

Declarations:

Availability of data and materials

All data underlying the results are available as part of the article and no additional source data are required.

Conflict of Interests Statement

The authors have no conflict of interests to disclose with any of the material presented within the manuscript.

Authorship

All authors discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with ethic guidelines for case reports of our institution - Ethics Committee of University of Catania, Policlinico-San Marco Hospital. Patients' anonymity was guaranteed. The principles of the Helsinki Declaration form were respected. Written informed consent was obtained from the patient regarding the publication of this case and related images.

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