

Successful Pregnancy in a Patient with Atypical Cogan's Syndrome

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Cogan's syndrome (CS) is a rare chronic inflammatory autoimmune disorder of unknown etiopathology and not clearly defined treatment strategies. CS is characterized by inflammatory eye disease and vestibular auditory symptoms affecting mainly young Caucasian adults of either gender, without a hereditary pattern. The classic form of CS, characterized by bilateral ocular involvement, primarily non-syphilitic interstitial keratitis and bilateral audiovestibular involvement resembling Meniere's disease, was first recognized as a separate clinical entity by David Cogan in 1945 [1]. There is usually an interval of less than 2 years between the onset of ocular and audiovestibular manifestations [1].

Atypical CS has numerous inflammatory ocular manifestations that are either isolated or associated with interstitial keratitis; these include episcleritis, scleritis, retinitis, chorioiditis, optical neuritis, glaucoma, papillary edema, cataracts, central retinal artery occlusion, xerophthalmia, ptosis and tendonitis. Unlike the classic form, in atypical CS the time interval between the onset of typical ocular and audiovestibular manifestations is usually 2 years at least. To the best of our knowledge, based on a computerized MEDLINE search, there are only four cases in the international literature of pregnancy with CS, but none with atypical CS [2-5].

PATIENT DESCRIPTION

We report a 33 year old Caucasian woman who presented to our department with a

previous diagnosis of atypical CS at 6 gestational weeks. In 2006 (3 years before her pregnancy) she suffered from Meniere-like vestibulitis symptoms with vertigo, hearing loss and tinnitus in the right ear. Following otorhinolaryngologic examination, treatment with corticosteroids and hyperbaric oxygen was begun but was unsuccessful. In January 2007, she reported photophobia and ocular pain, only in the right eye, associated with serosal central chorioretinitis and retinal pigment epithelium alteration. Otorhinolaryngological evaluation showed deafness in the right ear and severe sensorineural hearing loss in the left ear. A recent Epstein-Barr virus infection was detected.

In April 2007, atypical CS was diagnosed and she began a therapeutic protocol based on methotrexate, cyclophosphamide, cyclosporine, acetylsalicylic acid, corticosteroids and folic acid. Neurological evaluation, brain SPECT, echocardiogram and abdomen echography were in the normal range and all autoantibody tests were negative.

In 2009, planning her first pregnancy, she discontinued methotrexate and cyclophosphamide and began taking azathioprine. The immunosuppressive drug combination therapy comprised cyclosporine (300 mg per week), azathioprine (200 mg/week) and prednisone (15 mg/week), and aspirin (100 mg/daily). Due to worsening of the audiometric tests in her left ear, the immunosuppressive therapy could not be interrupted and the low dose multidrug immunosuppressive treatment was continued in an effort to reduce the teratogenic risk for the fetus should she become pregnant. The ophthalmic evaluation did not show any apparent clinical sequelae due to right chorioretinitis. She became pregnant in 2011 while on the same treatment. Due to increased risks of

both maternal and fetal complications, she was under intensive prenatal surveillance, i.e., every 4 weeks until the 32nd gestational week and then every 2 weeks until delivery. She was screened for malformations at 20 weeks. The ultrasound scan, performed at 32 gestational weeks, revealed fetal growth retardation with abdominal circumference below the fifth centile.

Her weight and blood pressure were recorded; laboratory tests performed at each visit were normal, as were audiometric, ophthalmic and cardiology examinations. The pregnancy had no relevant associated complications. The immunosuppressive therapy was not modified and a minimal improvement in auditory function of the left ear was recorded. The ultrasound scan, performed at 32 gestational weeks, revealed fetal growth retardation with an abdominal circumference below the fifth centile.

She was delivered by cesarean section at week 37 because of breech presentation and symmetric intrauterine growth restriction. The birth weight recorded was 2300 g. The average 1 minute and 5 minute Apgar scores were both 9. Histological examination showed a placenta measuring 16 x 15 x 3 cm and weighing 361 g with foci of intervillous necrosis. No congenital abnormalities were noted and the neonatal course was uneventful. Lactation was not advised based on international recommendations. Neither the mother nor the neonate had any postpartum complications. During the postpartum period, systemic prednisone (40 mg/day) was administered for 2 days and immunosuppressive therapy was increased to prevent relapse: cyclosporine (450 mg/week), azathioprine (400 mg/week) and prednisone (20 mg/week). During the 13 month postpartum follow-up period, the patient showed no signs of relapse.

Table 1. Key findings of Cogan syndrome and atypical Cogan syndrome during pregnancy

	Deliveliotou et al., 2007 [2]	Bakalianou et al., 2008 [3]	Currie et al., 2009 [4]	Tarney et al., 2014 [5]	Riboni et al., 2014
Type of syndrome	Cogan syndrome	Cogan syndrome	Cogan syndrome	Cogan syndrome	Atypical Cogan syndrome
Age (years)	39	39	33	24	33
Drugs	Ophthalmic steroids for 3 weeks (12–15 gw)	Ophthalmic steroids (12–38 gw)	Hydroxychloroquine 200 mg twice daily during pregnancy	None	Cyclosporine (300 mg/week) Azathioprine (200 mg /week) Prednisone (15 mg/week) Acetylsalicylic acid (100 mg/daily) during pregnancy
Change in symptoms	Interstitial keratitis developed at 12 gw	Interstitial keratitis developed at 12 gw	No change	Improvement in auditory and visual symptoms	Minimal improvement in auditory symptoms in left ear
Timing of delivery	38 gw in labor	38 gw in labor	Induction of labor at 38 gw for oligohydramnios	Induction of labor at 40+7 gw for expert opinion	Cesarean delivery at 37 gw for breech presentation and symmetric IGR
Mode of delivery	Spontaneous vaginal delivery	Spontaneous vaginal delivery	Cesarean delivery for non-reassuring fetal status	Caesarean delivery for non-reassuring fetal status	Cesarean delivery
Neonatal weight (g)	3820	None provided	3410	3680	2300
Postpartum complications	None	None	None	None	None
Follow-up after delivery	12 months	None provided	12 weeks	8 weeks	13 months

gw = gestational weeks, IGR = intrauterine growth restriction

COMMENT

Since Cogan's description of a "syndrome of non-syphilitic interstitial keratitis and vestibulo-auditory symptoms" in 1945, about 100 CS patients have been described in the literature [1]. The literature reports only four pregnancies associated with the classic form of CS [2-5] [Table 1], and this is the first report of pregnancy in a woman affected by atypical CS.

It was Deliveliotou et al. [2] who reported the first case of pregnancy in a woman with typical CS in 2007. Although the disease was inactive at conception, the patient had a relapse of ocular symptoms during the first trimester and was successfully treated with topical steroids. Her pregnancy course and delivery were uneventful. Bakalianou and co-authors [3] described the second case of pregnancy in typical CS in 2008, with a recurrent interstitial keratitis that required topical ophthalmic steroid treatment only. The patient had an uneventful full-term pregnancy. In a subsequent report by Currie et al. in 2009 [4], another pregnancy with CS was controlled well by low doses of hydroxychloroquine sulfate and prednisone. At 38 gestational weeks a cesarean delivery was performed for non-reassuring fetal status and arrest of dilatation in a labor induction for oligohydramnios. Tarney et al. in 2014

[5] showed an improvement in auditory and visual symptoms without therapy in a pregnant woman.

The potential effects of pregnancy on the natural history of the disease remain to be defined. In general, approximately 30% of pregnant women with autoimmune diseases will experience exacerbation of their disease during pregnancy and in the first 6 postpartum weeks if inadequately treated or if they have newly active disease [2-5].

The patient reported here had no relapse of either auditory or ocular symptoms during her pregnancy and maintained the same multidrug therapy she had started before conception. Preconception counseling was necessary to modify immunosuppressive therapy thereby eliminating drugs with potential teratogenic effects, as well as to quantify the overall risk of disease flare. A close follow-up during the course of her pregnancy was useful for both maternal and fetal monitoring. The maternal surveillance was in order to monitor ocular and vestibular auditory symptoms and identify any onset of systemic manifestations. The fetal monitoring assessed the potential effects of immunosuppressor and corticosteroid drugs, such as malformations, preterm birth, low birth weight and/or intrauterine growth restriction. Continuing the immunosuppressive and corticosteroid therapy was neces-

sary to stabilize auditory function and treat the vestibular auditory disease, as well as prevent the recurrence of ocular symptoms.

The paucity of cases in the literature does not allow conclusions to be drawn regarding the impact of pregnancy on the course of the CS, and vice versa. However, management of a pregnancy associated with inflammatory or autoimmune diseases such as CS requires a multidisciplinary approach which includes mandatory comprehensive evaluation of the disease before conception and close follow-up throughout the pregnancy to achieve a successful outcome.

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