CASE REPORT

Restoration of ovulation after unilateral ovariectomy in a woman with McCune–Albright syndrome: a case report

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Abstract

Introduction: McCune–Albright syndrome (MAS) is characterized by peripheral precocious puberty, *café-au-lait* spots, and polyostotic fibrous dysplasia. This syndrome is due to a post-zygotic mutation of the GNAS1 gene with mosaic distribution and unilateral predominance. Clinical manifestations depend on the tissues carrying the mutation. We describe the ovarian function before and after unilateral ovariectomy in a woman with MAS and bilateral distribution of the GNAS1 gene mutation. **Case report:** A 33-year-old patient, previously diagnosed as having MAS, presented irregular menstrual cycles (30–180 days) and monophasic temperature curves. Transvaginal ultrasound and blood tests were repeated at 3-day intervals over 3 months. Findings included a persistent quiescent left ovary, a persistent polycystic right ovary, constantly high estradiol-17 β (E₂) levels, and very low FSH and LH levels. She also presented severe persistent pelvic pain. Because of unilateral ovarian activity, a unilateral right ovariectomy was performed as well as biopsy of the remaining left ovary. A GNAS1 gene mutation was identified in both ovaries. A regular monthly menstrual cycle was immediately restored. On day 3 of the menstrual cycle, E₂ level was 30 pg/ml, FSH level was 7.5 mIU/ml, and LH level was 6.4 mIU/ml. On day 17, pelvic ultrasound showed one follicle of 25 mm in the left ovary. On day 21, the progesterone level was 13.1 ng/ml.

Discussion: This is the first report of ovulation being restored following unilateral ovariectomy in an adult patient suffering from severe MAS with GNAS1 gene mutation identified in both ovaries.

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Introduction

McCune–Albright syndrome (MAS) is a sporadic disease characterized by endocrine hyperfunctions, *café-au-lait* spots, and polyostotic fibrous dysplasia. Girls are preferentially affected (1). The most frequent endocrine presentation in MAS is gonadotropin-independent precocious puberty in girls. Precocious puberty is due to autonomous ovarian hyperfunction with low gonadotropin levels (2). Other hyperfunctional endocrinopathies include hyperthyroidism, autonomous adrenal hyperplasia, secreting pituitary adenomas, and hypophosphatemic osteomalacia (1).

MAS was first described separately by McCune (3) and Albright (4) in 1937. It was not until the early 1990s that Gs protein activation and cell hypermetabolism caused by a post-zygotic activating somatic mutation of the GNAS1 gene (5, 6) were found in a variety of tissues from patients with MAS (7) and correlated with the clinical features of the disease. The

mutation *fight* is a codon R201 which suppressed GTPase activity and continuously activates Gs. The Gs protein is a component of the cAMP signal transduction system (5). A receptor and an effector are the other two components of this transduction system. In non-mutant cells, the hormone linked to the receptor activates the Gs protein which in turn activates adenylate cyclase (thereby increasing target cell metabolism). In mutant cells, the Gs protein is thus activated without hormonal signal. The mutation has a mosaic distribution with unilateral predominance (8, 9) due to the post-zygotic occurrence of the GNAS1 mutation (10). The clinical manifestations of MAS vary in terms of time of occurrence, severity, and extension, and depend on the developmental stage at which the mutation occurs during embryo life and therefore the tissues involved in mutation.

MAS is well-known to pediatric physicians but few data exist on the follow-up of girls with MAS into adulthood. Regarding the gonadal function, only a few

reports about fertility and regular menses are available (11, 12). Anovulatory cycles and irregular menses have also been described (13, 14). Laven *et al.* (13, 15) were the first to report on the dynamics of ovarian function and management of infertility with unilateral ovariectomy in an adult woman with unilateral MAS.

Our report describes the successful restoration of ovarian function and ovulation after unilateral ovariectomy in a woman with severe MAS in which the GNAS1 mutation was identified in both ovaries.

Case report

A 33-year-old patient previously diagnosed as having MAS attended our outpatient clinic for fertility counseling. She presented the typical clinical triad with polyostotic fibrous dysplasia predominantly in the bones on the left side, *café-au-lait* spots also predominantly located on the left side, and precocious puberty when she was 8 years old. Data on treatment of precocious puberty and subsequent menses were not available. The patient reported regular menstrual cycles until the age of 21. At 21, she took oral contraceptive (OC) pills until the age of 31 with regular bleeding. When she discontinued the OC, menstrual cycles became irregular with oligomenorrhea (cycle: 60–180 days). Temperature curves were monophasic. There was no pain during menstruation. On physical examination, her height was 160 cm and weight 57 kg. Pubic hair, breast development, and external genital appearance were Tanner stage V. At the time of referral, increased serum estradiol-17 β (E_2 ; 722 pg/ml), low follicle-stimulating hormone (FSH; <1 mIU/ml), low luteinizing hormone (LH; <0.5 mIU/ml), normal prolactin (182 μ U/ml), normal androstenedione (1.50 ng/ml), and normal testosterone (0.19 ng/ml) levels were recorded. On transvaginal pelvic ultrasound, four cysts (23, 17, 16, and 11 mm) were observed in the right ovary alone. No cyst was observed in the left ovary. Endometrial lining thickness was 5.7 mm.

Transvaginal ultrasound and blood tests were repeated at 3-day intervals over 3 months. Serum was assayed for FSH, LH, progesterone, and E_2 . The results, presented in Figs 1–3, showed a persistent quiescent left ovary, a persistent multicystic right ovary, constantly high E_2 levels (200–900 pg/ml), and very low FSH and LH levels. At the 11th day, the progesterone level testified to a probable ovulation on the right ovary (the left ovary remained quiescent) (Fig. 1). The mechanism of this single ovulation remained misunderstood.

After a 60-day assessment period, a reduction in the E_2 level led to lesser negative feedback control of the pituitary–gonadal axis and higher FSH and LH levels, but no ovulation was observed in the left ovary.

The patient eventually ended the relationship with her partner and put off her plans to have a baby. One year later, she presented with severe pelvic pain. Pelvic ultrasound showed an enlarged multicystic right ovary (75 $\times$ 45 $\times$ 40 mm) and a cyst-free quiescent left ovary

Figure 1 Estradiol levels (E_2 , pg/ml) and progesterone levels (P, ng/ml) over 3 months.

(20 $\times$ 15 $\times$ 15 mm). High serum E_2 levels (800 pg/ml) and very low FSH and LH levels were found again.

The pelvic pain and the hyperstimulated right ovary were persistent. The option of a right unilateral ovariectomy was discussed extensively with the patient and the risk of a persistent abnormal ovarian function after the procedure was carefully explained. Subsequently right unilateral ovariectomy and left ovarian biopsy were performed by laparoscopy under general anesthesia. Just before laparoscopy, pelvic ultrasound showed a compatible follicular structure (20 mm) on the left ovary for the first time. Several right ovarian cysts and one left ovarian cyst were punctured separately using transvaginal ultrasound guidance. Endometrial biopsies were taken using operative hysteroscopy. Samples were taken from the left and right side of the endometrium.

Sections of the right ovary were prepared and embedded in paraffin. Thin sections measuring 10 μ m were prepared and stained with hematoxylin and eosin. Microscopic analysis of the right ovary showed primordial, primary, and secondary follicles along with Graafian follicles. All stages of follicular development were observed and the larger follicles were luteinized.

Figure 2 FSH and LH levels (mIU/ml) over 3 months.

Figure 3 Ultrasound findings (number and size of follicles in both ovaries) over 3 months.

DNA was extracted from blood lymphocytes, the endometrium, left and right ovarian tissues, and fluid obtained from ovarian follicles and cysts using commercial kits (Qiagen). PCR was performed on extracted DNA samples. A method described previously (9, 16) for selective enrichment of mosaic Arg 201 mutations was used. The *GNAS1* gene mutation (R201H) was identified in all the collected tissues, even in the left ovarian tissue and left cyst fluid. The method for selective enrichment of mosaic Arg 201 mutations cannot be considered as quantitative due to the repetition of nested PCRs. Nevertheless, the level of mutation reported in the left ovary was reproductively much lower than in the right one (data not shown), suggesting that the number of affected cells was indeed lower in the left ovary.

The patient recovered rapidly after the operation, and a regular monthly menstrual cycle was immediately restored. Five months later, on day 3 of her menstrual cycle, the E_2 level observed was 30 pg/ml, FSH level was 7.5 mIU/ml, and LH level was 6.4 mIU/ml. Pelvic ultrasound showed two follicles with diameters of 9 and 7 mm on the left ovary. On day 10, the E_2 level was 107 pg/ml. On day 17, the E_2 level was 445 pg/ml with one follicle of 25 mm and one follicle of 11 mm on the left ovary. On day 21, the progesterone level was 13.1 ng/ml.

Now, 3 years later, the patient has no plans to have a baby. Her menstrual cycles are still regular.

Discussion

This case represents the second longitudinal assessment of ovarian dysfunction in a woman suffering from MAS (13). Although similar to the case reported by Laven *et al.* one important difference was the identification of the mutation in both ovaries. Nevertheless, ovulation was restored with unilateral ovariectomy (15). The mutation was identified in all examined tissues including blood samples in the current case. These findings are rarely observed in McCune–Albright patients (8, 9).

Laven *et al.* (15) suggested that an *in vivo* test using a gonadotrophin-releasing hormone (GnRH) agonist may be useful for investigating whether the lesser or

non-affected ovary in McCune–Albright patients responds normally to reduced gonadotropin stimulation. No GnRH agonist *in vivo* test was used in the present case. Our patient's left ovary remained quiescent with no follicles throughout the 3-month assessment of ovarian dysfunction. The first follicle on the left ovary was observed on the day of laparoscopic ovariectomy. The disappearance of follicles on the left ovary with GnRH agonist treatment could not be observed in the present case as the left ovary was still quiescent with no follicles throughout the 3-month period. FSH and LH levels remained low during the 3-month assessment due to the negative feedback of the high E_2 level. Because autonomous activity in the left ovary was never shown, the mutation was believed to be absent or only weakly expressed in this ovary and hope was placed in the benefits of a right unilateral ovariectomy.

In the present case, the mutation was found in both ovaries on DNA analysis. Although the method used does not allow for precise quantification of the number of mutant cells, the repeated comparisons between ovaries clearly showed a much lower mutation level in the left ovary. In the cyst fluid, this variation was not observed between the two sides. This provides further evidence of the mosaic distribution of *GNAS1* gene mutation. In endometrial samples taken by biopsies, the mutation was localized on both sides of the uterus with a predominance on the right side.

We reported that polyostotic fibrous dysplasia was predominantly located in the bones on the left side and *café-au-lait* spots were also predominantly located on the left side, despite the fact that the left ovary had a lower mutation level.

Following the right ovariectomy, the normal function of the remaining left ovary with ovulatory cycles provided evidence of central GnRH control of normal cells. The mutant cells in the left ovary appeared to be quiescent with no hyperfunction at this time. Minimal number of mutant cells seems to be necessary to result in autonomous function. In this case, this number is not reached at all after unilateral ovariectomy and normal function can be restored. Preferential removal of the mutant ovary seemed to create a new balance between mutant cells and non-mutant cells. This new balance allowed expression of non-mutant cells as some girls are affected with MAS but have normal puberty following autonomous ovarian activity and reproduce normally thereafter (11). This would also be an explanation why previously irregular MAS patients, develop spontaneously regular cycles and subsequently conceive. Unilateral ovariectomy restored gonadotropin control in both our patient and Laven's patient (15). But, there is another hypothesis about cell cycle differences between mutated and normal cells. Indeed, in an ovary of a MAS patient, mutated cells could be eventually recruited in a similar way to normal cells. Thus, there is a risk of activation of mutant cells with high E_2 levels,

anovulatory cycles, and irregular menses in the present case. Regulation of the expression of mutant cells warrants further research.

This observation reinforces the necessity of a careful monitoring of follicular development in the ovaries of women with MAS. In series, the resumption of ovulation may be followed by pregnancy such as in the Dutch case, with a potential transmission genetic abnormality. This has never been described thusfar probably because of the lethal effect of the mutation.

In conclusion, the present report provides evidence for the possibility of autonomous reactivation of unilateral ovarian function in a 33-year-old McCune–Albright patient. It also shows that normal ovarian function in McCune–Albright patients can be restored through unilateral ovariectomy even if the GNAS1 gene mutation is present in the quiescent ovary. The risk involved is activation of mutant cells in the remaining ovary. The physiopathological regulation of the expression of normal cells and mutant cells warrants further research.

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