Alport syndrome with pelvic leiomyomatosis: The role of hormonal suppression

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ABSTRACT

Introduction: Alport syndrome with diffuse pelvic leiomyomatosis is a complex combination for which the course of treatment is not well described. This case describes the outcomes of a trial with gonadotropin-releasing hormone analogues as an alternative to extensive surgery.

Case Report: A 47-year-old female patient, known with Alport syndrome associated with diffuse leiomyomatosis, was referred to our gynecological service because of a pelvic mass. The patient complained of obstipation and pain in the right hypochondrium. Magnetic resonance imaging showed a diffuse multi-lobulated leiomyomatosis from the vulvar to the perineal area. As the removal of the mass would imply very extensive surgery, conservative treatment options were searched for, in analogy with the medical treatment of uterine leiomyomas. A few trials used gonadotropin-releasing hormone analogues in the treatment of diffuse pelvic leiomyomatosis but follow-up data of these articles are lacking. For this patient, who was close to menopausal age, a trial therapy with gonadotropin-releasing hormone analogues was followed by an adnexectomy for total hormonal suppression. The patient’s follow-up showed stabilization of the mass and decrease of the pain complaints.

Conclusion: This case demonstrates that hormonal suppression can be a successful alternative to complex surgery in a case combining Alport syndrome and diffuse pelvic leiomyomatosis.

Keywords: Alport syndrome, Diffuse leiomyomatosis, GnRH analogues, Pelvic leiomyomatosis

INTRODUCTION

Alport syndrome is a rare genetic disease that results from mutations in genes encoding for type IV collagen. The exact prevalence is not very well known, yet it is estimated to affect one in every 50,000 live births worldwide [1–3].

The classical presentation of Alport syndrome includes renal manifestations, ocular abnormalities, and sensorineural hearing loss. However, it has been reported that 2–5% of patients with X-linked Alport syndrome present diffuse leiomyomatosis, in which smooth muscle cells can overgrow, most often in the esophagus but also in the respiratory and female reproductive tracts [1, 2, 4].

The transmission of Alport syndrome can be X-linked, autosomal dominant or autosomal recessive [1, 5]. The X-linked transmission accounts for the majority of affected patients, about 80%, and is due to mutations in the COL4A5 gene on the X chromosome [1–3]. Some
patients have a chromosomal microdeletion at the 5' ends of COL4A5, which extends into the adjacent COL4A6 gene. This phenotype can be associated with diffuse leiomyomatosis [6–9]. The relationship between deletions of the 5’ end of the COL4A6 gene and the pathogenic formation of leiomyomas is not well understood. One hypothesis suggests that this association of deletions cause dysregulation of neighboring genes, contributing to smooth muscle overgrowth [4, 5].

The treatment of diffuse leiomyomatosis is not straightforward. Complete surgical resection may imply very extensive surgery, hence the importance of exploring conservative treatment options.

CASE REPORT

The patient, a 47-year-old woman, was referred to our university hospital through the urology department, because of obstipation and the finding of a large pelvic mass on imaging. Her medical and surgical history revealed a known X-linked Alport syndrome and diffuse leiomyomatosis. Genetic testing confirmed that she carries a pathogen deletion of at least exon 1 in the COL4A5 gene and exon 1 and 2 in the COL4A6 gene. Due to leiomyomatosis in her esophagus, she underwent an esophagectomy followed by reconstruction in our center at the age of 17. When she was 24 years old, she had an uncomplicated vaginal delivery of a daughter. At the age of 31, a vulvar leiomyoma was resected. One year later she had a nerve sparing clitoral reduction due to isolated clitoromegaly—pathology confirmed the presence of a leiomyoma. Finally, at the age of 35 she underwent a total non-radical hysterectomy through laparotomy for a myomatous uterus. Other elements in her medical history included chronic obstructive pulmonary disease, depression, arterial hypertension, and microscopic hematuria.

Both her mother and daughter have been diagnosed with Alport syndrome as well. Her daughter, now 22 years old, also underwent an esophagectomy and partial vulvectomy because of diffuse leiomyomas.

At the time of referral to our service, the patient had undergone extensive investigations. A computed tomography (CT) scan of the abdomen had showed a retropubic unspecific nodule of 3 cm diameter and calcifications in the left outer labium. A colonoscopy and gastroscopy did not report abnormalities. An additional magnetic resonance imaging (MRI) showed a diffuse multi-lobulated mass extending from the vulvar to the perineal area (Figures 1–3).

The nodules were located anteriorly and posteriorly to the pubic symphysis, some being scattered. The most evident nodule was found anteriorly and to the right of the urethra and measured 2.3 by 2.6 by 2.2 cm. There was urethral and clitoral involvement, which extended to the right outer labium.

At this point a transvaginal biopsy and cystoscopy under general anesthesia was proposed to obtain pathological
diagnosis. The vaginal biopsy confirmed the presence of a leiomyoma, with no signs of malignancy. Estrogen and progesterone receptors were positive. After the results were known, the patient was sent for gynecological examination to discuss treatment options.

The clinical examination could only reveal the known clitoromegaly and a solid but non-painful soft tissue mass of approximately 2.5 cm anteriorly to the vaginal wall, along the whole trajectory of the urethra. This could also be visualized on transvaginal ultrasound (Figure 4). There was no impact on the vagina, nor did the patient express discomfort. The patient reported more lower abdominal pain since the tru-cut biopsy.

Figure 4: Sagittal transvaginal ultrasound image of the leiomyoma, anterior to the urethra.

Figure 5: Sagittal transvaginal ultrasound image of the leiomyoma after treatment with GnRH analogues for two months and adnexectomy.

The patient was discussed in multidisciplinary conference. Removal of the mass would imply very extensive surgery, resulting in the need of a uro- and colostomy. To avoid this operation, considering her age, a trial with gonadotropin-releasing hormone (GnRH) analogues was proposed, knowing that leiomyomas are hormone-dependent and could possibly shrink at menopause. In this scenario, a bilateral adnexectomy would ensure that the patient remains in menopause.

After two months of treatment with GnRH analogues a new MRI showed stable findings. The patient noticed a global improvement of the pain and agreed to proceed to a bilateral adnexectomy. It was discussed pre-operatively that during laparoscopy the pelvic leiomyomas would most likely not be visible nor easily accessible and therefore would not be explored or removed, as it could only lead to complications.

Vaginal examination during narcosis did not reveal additional findings. At laparoscopy, adhesions were seen in the upper abdomen, secondary to previous surgery. As thought, no pelvic abnormalities were seen during surgery and the pelvic leiomyomas were not visible. Both adnexa were removed uneventfully and sent for pathology analysis. As the patient expressed very little to no menopausal complaints during treatment with GnRH analogues, it was not deemed necessary to start hormonal replacement therapy after surgery. Pathology examination of the adnexa showed no signs of leiomyomatosis, and only a small spot of endometriosis on one fallopian tube.

At six weeks and three months follow-up, the patient reported a decrease of pelvic pain with remaining discomfort mostly associated with physical activity. Some feeling of pressure in the lower abdomen persisted with occasional difficulties to completely empty the bladder. There were no gastrointestinal complaints. On transvaginal ultrasound, the leiomyoma anteriorly to the urethra was still visible with a decrease of maximum diameter from 2.5 to 2.2 cm (Figure 5).

It was agreed to pursue further expectant management with close monitoring of the patient. The one-year follow-up showed a stable leiomyoma on imaging and a decrease of the pain complaints, with the exception of a small residual discomfort during physical activity. A new gastroscopy and positron emission tomography scan showed no abnormalities.

**DISCUSSION**

The association of Alport syndrome with leiomyomatosis has already been described in 1983 by Garcia-Torres [10]. This pathology mostly starts in the esophagus at a young age—around the age of six years in men and 14 years in women. In most cases the vulvar-perineal disease appears after puberty and is often localized next to the clitoris—as it was the case in our patient. The literature does not describe perineal lesions in men [11].

Alport syndrome with diffuse leiomyomatosis is a complex combination that does not have a specific course of treatment. Due to the extensive nature of the leiomyomatosis in our case, surgery would be very radical and therefore we needed to explore alternative options comparing them with uterine leiomyomas.
Uterine leiomyomas are very common in reproductive-age women. Therapeutic possibilities include expectant management, medical therapy, or surgery. Treatment of leiomyomas kicks in when there are issues of bleeding, bulk symptoms, reproductive dysfunction, or pain [6]. Medical therapy includes the use of (estrogen-) progestin contraceptives, progestin-releasing intrauterine devices (IUDs) and GnRH analogues. Surgical therapy of leiomyomas includes hysteroscopic or laparoscopic myomectomy or hysterectomy.

Uterine leiomyomas in patients with Alport syndrome can be treated by a myomectomy, or hysterectomy if child desire is fulfilled. Pelvic leiomyomas, however, offer more problems as their therapeutic options are less described and investigated. We cannot simply compare them with uterine leiomyomas as they are often diffuse and originate from other organs such as the bladder, urethra, or rectum.

When considering conservative treatment options for uterine leiomyomas, (estrogen-) progestin contraceptives are not likely to make the tumor shrink but would mainly influence the symptoms, whereas GnRH analogues act centrally and are associated with hypoestrogenic side effects. Numerous data have shown that GnRH analogues decrease the volume of leiomyomas [6, 12]. Only a few trials tried to use GnRH analogues in the treatment of patients with Alport syndrome and diffuse leiomyomatosis [13, 14]. The abstract of Burgos et al. explains that they aimed at using GnRH analogues to shrink a tumor in the genito-pelvic region to be able to extirpate it with the highest likelihood of success [13]. Unfortunately, this article does not describe the results of this treatment nor follow-up data. The report of Taraschi et al. describes the case of a premenopausal woman presenting with a benign leiomyoma on the right side of the clitoris [14]. Unfortunately, the patient refused genetic testing to rule out Alport syndrome and GnRH analogues were not tried in this case.

In the literature other trials described the use of GnRH analogues for patients that have intravenous leiomyomatosis, benign metastasizing leiomyoma, and pulmonary lymphangioleiomyomatosis. These cases showed a positive impact following treatment, as the leiomyomatosis is hormone-dependent and therefore answers to a treatment that puts a patient in menopause [15–18].

CONCLUSION

This case illustrates that a treatment based on GnRH analogues can be a valid alternative to invasive surgery for diffuse leiomyomatosis in a patient with Alport syndrome. This trial appeared to be successful in stabilizing the disease and related complaints. Since the patient was close to menopausal age, an adnexectomy for total hormonal suppression was, as a next step, deemed appropriate. The one-year follow-up showed a global improvement since the start of the GnRH analogues that remained after removal of the adnexa.

REFERENCES


Author Contributions
Céline Verougstraete – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Karel Decaestecker – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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