Clinical Case Reports

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CASE REPORT

Virginal breast hypertrophy in a patient with Beckwith–Wiedemann syndrome

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Key Clinical Message

Virginal breast hypertrophy is a multidisciplinary condition including surgical, pediatric, and endocrine/gynecological disciplines, and its successful diagnosis and management requires complex, team approach.

Keywords

Beckwith–Wiedemann syndrome, Gigantomastia, virginal breast hypertrophy.

Introduction

Beckwith–Wiedemann syndrome (BWS) is the most common overgrowth disorder usually present at birth, characterized by an increased risk of embryonal tumors, such as nephroblastoma, neuroblastoma, hepatoblastoma, or rhabdomyosarcoma. We report an 11-year-old girl with BWS, adrenal insufficiency, growth deficiency, mild–moderate mental retardation, cardiomyopathy, and surgical history (bilateral adrenalectomy, hemangiectomy, and orthopedic surgery) who developed virginal breast hypertrophy (VBH). The patient has undergone total mastectomy after complex multidisciplinary consultation and literature review. As VBH is a multidisciplinary condition including surgical, pediatric, and endocrine/gynecological disciplines, its successful diagnosis and management requires complex, team approach.

Beckwith–Wiedemann syndrome (BWS) is the most common overgrowth disorder in infancy which was first described by Hans-Rudolf Wiedemann in 1964 and named EMG syndrome due to its core/underlying symptoms: exomphalos, macroglossia, and gigantism [1]. In 1969, J. Bruce Beckwith from Loma Linda University described more cases of this syndrome and the name Beckwith–Wiedemann syndrome was then generally acknowledged in honor of both physicians [2, 3].

Beckwith–Wiedemann syndrome usually presents at birth and is characterized by macrosomia, macroglossia, ear creases or ear pits, organomegaly, omphalocele, neonatal hypoglycemia, renal abnormalities, and an increased risk of embryonal tumors, such as Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma [4, 5]. In 24% of cases, hemihypertrophy is present [6].

The pattern of inheritance is complex and includes both autosomal dominance with variable expressivity, contiguous gene duplication at 11p15, genomic imprinting due to a defective or absent copy of the maternally derived gene at 11p15, and mutations of the gene in the region of chromosomes 11p15 and 5q35 [7].

Although children with BWS are much more likely (about 600 times more than other children) to develop certain childhood cancers (listed above) [8], only five reports of benign breast tumors in patients with BWS have been reported so far [9–13].

Virginal breast hypertrophy (VBH) is a rare benign condition characterized by rapid and massive enlargement of one or both breasts usually during peripubertal period [14]. Neither etiology nor treatment is known; however, a hypersensitivity of the breast to normal levels of estrogens has been proposed as its cause [15]. Recommended treatment methods include subcutaneous mastectomy with silicone prosthesis application, reduction mammoplasty, hormone therapy, and combinations of these, pharmacological and surgical, managements [16].

Here, we report an 11-year-old girl with BWS, adrenal insufficiency, growth deficiency, cardiomyopathy, mild mental retardation, and surgical history (bilateral adrenalectomy, liver hemangiectomy, and orthopedic surgery) who developed VBH.

Case Report

The patient, an 11-year-old girl now, the first child of unrelated parents of Polish origins, was born as a preterm infant at 33 Hbd = hemoglobin with body mass of 1500 g (−1.5 SDS), body length of 43 cm (−0.9 SDS), and cardiomyopathy diagnosed prenatally. At the age of 7 days, she required mechanical ventilation due to respiratory insufficiency. Since the age of 1 month, hyperinsulinemic hypoglycemia was diagnosed and treatment with diazoxide was commenced. Additionally, the girl presented with microcephaly, left-sided hemihypertrophy, dysmorphia, small umbilical hernia, mild developmental delay, and organomegaly: enlarged liver, spleen, pancreas, and adrenal glands was found on CT scan. She was also diagnosed with liver hemangioma, which was removed during her infancy. Although neither growth advancement (in contrary – growth deficiency was observed) nor macrocephaly (in contrary – she had microcephaly) was present, a clinical diagnosis of incomplete BWS was established and confirmed then with molecular tests (see section "genetic studies").

When the girl was 2 months old, a bilateral retinal detachment was diagnosed and she had ophthalmologic surgery for that. At the age of 2 years 7/12, the patient underwent bilateral adrenalectomy due to the focal macronodular adrenal hypertrophy and since then has been on adrenal steroids supplementation. She has also had recurrent urinary tract infections and has been under nephrological observation for that.

By the age of 11 years, the patient rapidly developed massive enlargement of breasts with left-sided predominance; chest circumference at the breasts level was 86 cm.

Upon physical examination, the girl presented with a nontender redden but without inflammatory symptoms, bilateral with left-sided predominance, giant mass of the breasts, and mobile over the underlying tissues with stretch marks below them (Fig. 1). Peripheral lymph nodes were not enlarged. Serum α-fetoprotein and ß-HCG were not elevated.

Biochemical investigations including complete blood count, biochemistry, hormone panels: thyroid hormones (FT3, FT4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and progesterone were within normal range values.

LH-RH test demonstrated the following outcomes: an increase in serum FSH (from 7.56 to 14.5 IU/L), in serum LH (from 1.17 to 5.42 IU/L), and in estradiol <8 pg/mL (below pubertal level) (Table 1). Complete imaging assessment including breast and abdominal ultrasound

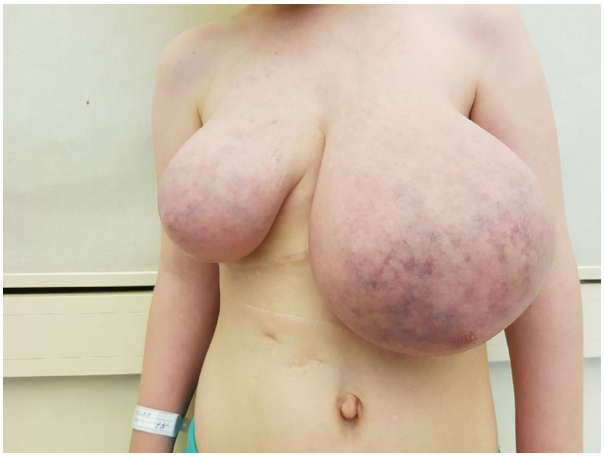

Figure 1. Preoperative features of the patient with virginal breast hypertrophy – just before mastectomy, discernible left-sided predominance.

Table 1. Patient's hormonal results

Parameter	Patient's results	Reference value
Estradiol	<8 pg/mL	Folicular period: 25–100 pg/mL Luteal period; 20–220 pg/mL
FSH	3.28 IU/L	0.4–12.7 IU/L
LH	1.5 IU/L	0–0.9 IU/L
Prolactin	3.82 ng/mL	2.7–19.7 ng/mL
ACTH	14.7 pg/mL	10–6 pg/mL

and thoracic and brain MRI was performed (see section "imaging studies"). First-line medical management consisted of anti-inflammatory medications and antibiotics with no clinical improvement. Surgical biopsy of both breasts was performed with histopathologic examination which did not demonstrate neoplasia (see section "histopathologic examination").

Following multidisciplinary consultation, after complex literature review and evaluation of risks and benefits, the patient was qualified to total mastectomy. The mother gave the informed consent, and the surgery was performed with success.

Genetic studies

- Serum-derived DNA: chromosome 11 – paternal isodisomy with no evidence of mosaicism (a faint maternal allele)/
- MLPA for LIT1, H19 I IGF-2: abnormal methylation pattern = complete paternal isodisomy
- Fibroblasts: normal biparental inheritance/hair root cells: paternal only contribution to the DNA

Imaging studies

Breast ultrasound

The breasts of typical, glandular texture, most of the gland tissue located peripherally, hypoechogenic, heterogenous areas within central parts of the glands predominantly within the left breast. Lactary ducts not widen.

Abdominal ultrasound

Postresection state of the right lobe of the liver due to the liver angioma within fourth lobe of the liver, the liver enlarged within the left lobe, homogenous without focal abnormalities. Pot cholecystectomy state. The pancreas, the spleen, and the bile ducts normal. The kidneys apart from slightly hyperechogenic pyramids and little cysts within the cortex, normal. Postbilateral adrenalectomy state.

Gynecological ultrasound

Infantile uterus, length of 5.9 cm, anterior–posterior (AP) dimension – 11.4 mm endometrium not apparent. Dimension of left ovary: 29 × 15 mm, of right ovary: 27 × 14 mm, small cysts within both ovaries.

Thoracic MRI

Significant asymmetry of the breasts; the left one significantly larger. The gland tissues located mostly peripherally, abnormal, heterogeneous areas within the central part of the glands. No features of the inflammation or abscesses.

Direct Citations

Figure 2. Surgical biopsy revealed overgrowth of fibrous tissue and single glands with presence of benign ductal proliferation (usulal ductal hyperplasia, UDH). Original magnification ×100.

Figure 3. Immunohitochemical stains were not heterogenous - up to 80% in the stroma cells with faint to moderate intensity and up to 20% in glandular cells with faint to moderate intensity.

A. Progesterone - Original magnification ×200.

B. Estrogene - Original magnification ×200.

Figure 4. Surgrical material - bilateral giant fibroadenomas.

A. Original magnification ×100

B. Original magnification ×100

Discussion

We report a female patient with BWS and VBH. According to the criteria by Choufani et al. [17], the diagnosis of BWS is established upon the presence of minimum three major criteria (macrosomia, macroglossia, umbilical hernia, visceromegaly involving liver and pancreas, and hemihyperplasia) and minimum two minor criteria (neonatal hypoglycemia and dysmorphic features). Our patient presented with clinically incomplete but genetically confirmed BWS (complete paternal isodisomy in LIT1, H19, and IGF-2 genes); instead of growth advancement, growth deficiency was observed, and instead of

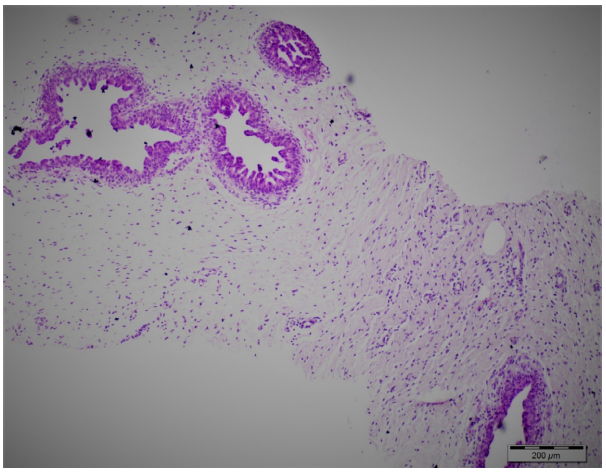

Figure 2. Surgical biopsy revealed overgrowth of fibrous tissue and single glands with presence of benign ductal proliferation (usual ductal hyperplasia, UDH). Original magnification x 100.

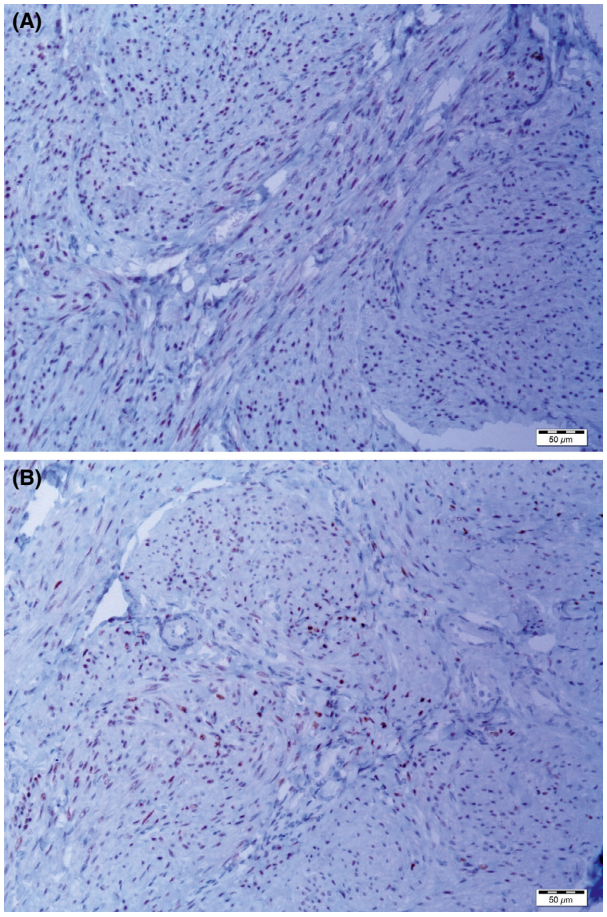

Figure 3. Immunohistochemical stains were not heterogenous – up to 80% in the stroma cells with faint to moderate intensity and up to 20% in glandular cells with faint to moderate intensity. (A) Progesterone – Original magnification x 200. (B) Estrogen – Original magnification x 200.

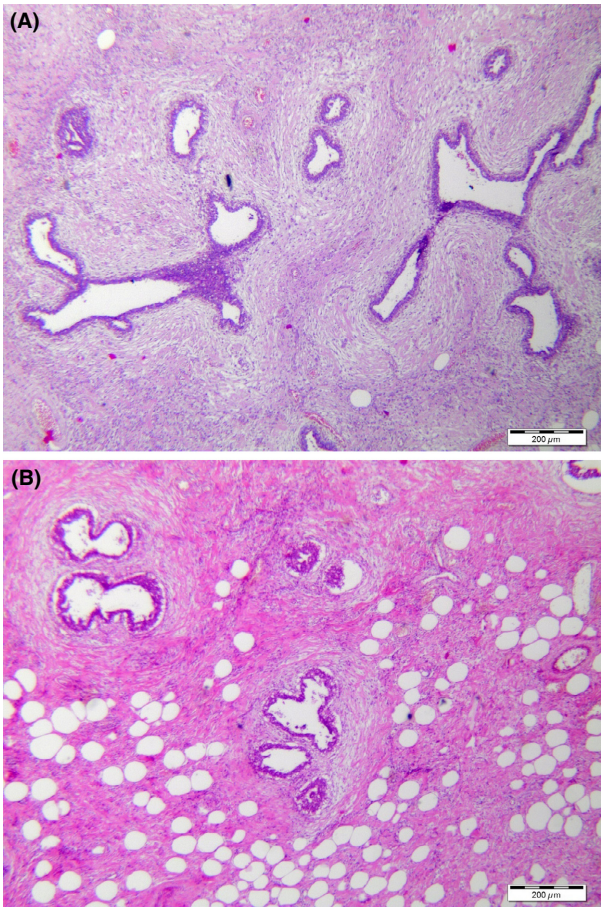

Figure 4. Surgical material – bilateral giant fibroadenomas. (A) Original magnification x 100. (B) Original magnification x 100.

macrocephaly, she had microcephaly. Moreover, her medical history was very complicated. Beside BWS, our patient had adrenal insufficiency following bilateral adrenalectomy due to the focal macronodular adrenal hypertrophy and has been on corticosteroids supplementation. Additionally, she presented with growth deficiency, cardiomyopathy (treated with propranolol and verospiron) and has undergone three surgeries. Typically for BWS characterized by transient hypoglycemia in 50% of cases and persistent hypoglycemia in 5% of patients [18], the girl had hypoglycemia with hyperinsulinism since infancy and has been treated with diazoxide till the last visit at hospital when the therapy was discontinued with normoglycemia maintained.

There is an increased risk of embryonal tumors in BWS [8], but five case reports of benign breast tumors in female adolescents with this syndrome have been published [9–13]. Similarly to our patient, these were mostly asymmetric lesions, and no increase in oncological biomarkers was reported. The applied medical strategy was surgical removal of the benign tumor. In our case, however, the patient did not have any tumors, but VBH was diagnosed, which is also a rare condition of unknown etiology characterized by rapid and massive enlargement of one or both breasts usually during peripubertal period [19]. There are few theories concerning the cause of VBH, but the most popular one postulates the end-organ hypersensitivity to normal circulating levels of estrogen in the body [20]. In the study by Morimoto et al. [21], an increased estrogen receptor staining by immunohistochemistry in the fibroadenoma-like nodules resected from both breasts of the patients with VBH has been reported. However, in another study by Glisoci et al. [22], no increase in estrogen or progesterone receptors has been demonstrated. Therefore, it seems that the estrogen theory for dysregulated breast growth is more complex, and includes not only increased estrogen receptor density in the breast tissue, but also an excess local estrogen production, abnormal estrogen receptor sensitivity, and, possibly,

the presence of an estrogen-like substance in the body, which stimulates receptors when normal level of estrogens is present [20].

In our case, the expression of estrogen receptors within breast tissue was heterogeneous: from low to moderate rate. However, it is important to point that our patient did not enter her pubertal period when breast hypertrophy appeared.

As the etiology of VBH is uncertain, and <100 patients with this condition have been reported in the literature, no treatment algorithm has been established so far. Recommended therapeutic methods include both pharmacological and surgical managements. Subcutaneous mastectomy with silicone prosthesis application, reduction mammoplasty, hormone therapy, and combinations of these has been applied in these patients [23].

Among these methods, however, surgical resection was the usual, most commonly commenced therapy. In some patients, especially in terms of total mastectomy, it was even a sufficient treatment alone [24]. Nonetheless, many case reports on this issue demonstrate the high rate of recurrence following reduction mammoplasty [25, 26]. Re-operation or postsurgical pharmacological treatment with anti-estrogen agent was applied in these cases. Although no outcomes suggest the superiority of one agent over the others, dydrogesterone and tamoxifen seem to be the most effective medications that have been used most commonly [27].

According to literature, the recurrence of breast growth following a reduction mammoplasty was in about 63% of cases, while it was only 2% when total mastectomy was performed [23].

These data rather support the need for complete removal of all breast tissue in VBH due to the considerable risk of continued growth in this condition.

When it comes to our patient, the decision on her medical management was a very difficult one. On the one hand, the breast enlargement was so rapid and massive that it might soon lead to skin atrophy. Not to mention skeletal complications and psychological issues. On the other hand, patient's medical and surgical history was very complicated. No such case has been reported in the literature so far. Not only did she had VBH, but also BWS which is associated with its own complications, such as an increased risk of neoplasma. Moreover, she did not enter puberty yet. Pharmacotherapy with anti-estrogen agent, tamoxifen, was excluded at the beginning, as this medication has many side effects such as an increased risk of endometrial cancer, hot flashes, increased risk of venous thrombosis, and bone density changes [28], which must be taken into consideration, especially in the adolescent with the positive history of hepatic condition (liver hemangioma, postsurgical state) and increased risk of tumors due to her underlying disease. A reduction mammoplasty seemed to be a good strategy, but again, in VBH, the recurrence rate is high and either re-operation or postsurgical maintenance pharmacotherapy is usually needed. With such complicated medical history exposing the patient to the second surgical intervention and anesthesia run a great risk, and anti-estrogen agents were disqualified due to the aforementioned reasons.

After complex literature search and a multidisciplinary consultation including endocrine, gynecological, surgical, radiology, and pathology disciples, the decision on total mastectomy was established. The mother gave the informed consent, and the surgery was performed with success.

Conclusions

Gigantomastia in adolescents is a multidisciplinary condition including surgical, pediatric, and endocrine/gynecological disciplines, and therefore, its successful diagnosis and management requires complex, team approach.

As the condition is rare and no treatment algorithm is established, medical management should be tailored to the patient – all risks and benefits must be taken into consideration and the final therapeutic decision should be established together with the patient and/or her caregivers.

Authorship

All authors have equal contribution in preparing and editing the text of this manuscript: its concept, form, and all figures and tables.

Conflict of Interest

None declared.

References

1. Wiedemann, H. R. 1964. Familial malformation complex with umbilical hernia and macroglossia-a new syndrome? J. Genet. Hum. 13:223–232.
2. Weksberg, R., C. H. Shuman, and J. B. Beckwith. 2010. Beckwith–Wiedemann syndrome. European Journal of Human Genetics 18:8–14.
3. Beckwith, J. 1969. Macroglossia, omphalocele, adrenal cytomegaly, gigantism, and hyperplastic visceromegaly. Birth Defects 5:188–196.
4. Spivey, P. S., and W. T. Bradshaw. 2009. Recognition and management of the infant with Beckwith-Wiedemann Syndrome. Adv. Neonatal Care 9:279–284.
5. Chen, C. P. 2007. Syndromes and disorders associated with omphalocele (I): Beckwith-Wiedemann syndrome. Taiwan J. Obstet. Gynecol. 46:96–102.

6. Elliott, M., R. Bayly, T. Cole, I. K. Temple, and E. R. Maher. 1994. Clinical features and natural history of Beckwith–Wiedemann syndrome: presentation of 74 new cases. Clin. Genet. 46:168–174.
7. Maas, S. M., F. Vansenne, D. J. Kadouch, A. Ibrahim, J. Bliek, S. Hopman, et al. 2016. Phenotype, cancer risk, and surveillance in Beckwith-Wiedemann syndrome depending on molecular genetic subgroups. Am. J. Med. Genet. A 170:2248–2260.
8. Mussa, A., C. Molinatto, G. Baldassarre, E. Riberi, S. Russo, L. Larizza, et al. 2016. Cancer risk in beckwith-wiedemann syndrome: a systematic review and meta-analysis outlining a novel (Epi)Genotype specific histotype targeted screening protocol. J. Pediatr. 176:142–149.
9. Raine, P. A., H. R. Noblett, B. W. Houghton-Allen, and P. E. Campbell. 1979. Breast fibroadenoma and cardiac anomaly associated with EMG (Beckwith- Wiedemann) syndrome. J. Pediatr. 94:633–634.
10. Labrune, B., M. Latrobe, J. J. Benichou, M. Robin, and A. May. 1988. Neonatal hyperinsulinism, congenital corporeal hemihypertrophy, tumor of the breast in adolescence. Arch. Fr. Pediatr. 45:413–415.
11. Bemurat, L., P. Gosse, P. Ballanger, P. Tauzin-Fin, P. Barat, D. Lacombe, et al. 2002. Successful laparoscopic operation of bilateral pheochromocytoma in a patient with Beckwith-Wiedemann syndrome. J. Hum. Hypertens. 16:281–284.
12. Poh, M. M., T. N. Ballard, and J. J. Wendel. 2010. Beckwith-Wiedemann syndrome and juvenile fibroadenoma: a case report. Ann. Plast. Surg. 64:803–806.
13. Cappuccio, G., A. De Crescenzo, G. Ciancia, L. Canta, M. Moio, and I. Mataro. 2014. Giant breast tumors in a patient with Beckwith-Wiedemann syndrome. Am. J. Med. Genet. A 164A:182–185.
14. Menekşe, E., S. Önel, F. Karateke, K. Daş, İ. Bali, H. Bozkurt, et al. 2013. Virginal breast hypertrophy and symptomatic treatment: a case report. J. Breast Health 10:122–124.
15. Güneş, D., K. Mutafoğlu-Uysal, T. Canda, S. Saydam, A. P. Cemeroğlu, and N. Olgun. 2008. Unilateral juvenile (virginal) hypertrophy of the breast. Turk. J. Pediatr. 50:278–281.
16. Griffith, J. R. 1989. Virginal breast hypertrophy. J. Adolesc. Health Care 10:423–432.
17. Choufani, S., C. Shuman, and R. Weksberg. 2013. Molecular findings in Beckwith-Wiedemann syndrome. Am. J. Med. Genet. Part C. 163C:131–140.
18. Flanagan, S. E., R. R. Kapoor, V. V. Smith, K. Hussain, and S. Ellard. 2011. Paternal uniparental isodisomy of chromosome 11p15.5 within the pancreas causes isolated hyperinsulinemic hypoglycemia. Front Endocrinol. 2:66.
19. Michala, L., A. Tsigginou, D. Zacharakis, and C. Dimitrakakis. 2015. Breast disorders in girls and adolescents. Is there a need for a specialized service? J. Pediatr. Adolesc. Ginekol. 28:91–94.
20. Dancey, A., M. Khan, J. Dawson, and F. Peart. 2008. Gigantomastia: a classification and review of the literature. J. Plast. Reconstr. Aesthet. Surg. 61:493–502.
21. Morimoto, T., K. Komaki, T. Mori, M. Sasa, H. Miki, H. Inoue, et al. 1993. Juvenile gigantomastia: report of a case. Surg. Today 23:260–264.
22. Gliosci, A., and F. Presutti. 1993. Virginal gigantomastia: validity of combined surgical and hormonal treatments. Aesthetic Plast. Surg. 17:61–65.
23. Hoppe, I. C., P. P. Patel, C. J. Singer-Granick, and M. S. Granick. 2011. Virginal mammary hypertrophy: a meta-analysis and treatment algorithm. Plast. Reconstr. Surg. 127:2224–2231.
24. Furnas, D. W. 1982. Subcutaneous mastectomy for juvenile hypertrophy of the breast: report of a case. Br. J. Plast. Surg. 35:367–370.
25. Pülzl, P., T. Schoeller, A. Tzankov, and G. Wechselberger. 2005. Unilateral breast enlargement 5 years after reduction mammaplasty. Aesthetic Plast. Surg. 29:404–406.
26. Ship, A. G. 1971. Virginal and gravid mammary gigantism-recurrence after reduction mammaplasty. Br. J. Plast. Surg. 24:396–401.
27. Sperling, R. L., and J. J. Gold. 1973. Use of an anti-estrogen after a reduction mammaplasty to prevent recurrence of virginal hypertrophy of breasts: case report. Plast. Reconstr. Surg. 52:439–442.
28. Lipov, E. G., J. R. Joshi, and S. Sanders. 2009. A new mechanism of action for tamoxifen. Lancet Oncol. 10:542.

