Penicillamine-induced virginal mammary hypertrophy

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Virginal mammary hypertrophy (VMH), also known as juvenile mammary hypertrophy, is characterized by excessive enlargement of the breasts. Especially in adolescent patients, this condition can cause a negative body image to develop and result in significant psychological stress. Furthermore, social problems can arise from difficulties in finding appropriately-fitting attire and having trouble exercising. Although the mechanism of VMH has not been fully elucidated, several associated drugs have been identified. In this report, we present a 15-year-old female patient with Wilson disease who developed macromastia after administration of penicillamine for 8 months. Despite cessation of penicillamine for 3 months, the condition remained stable; thus, reduction mammoplasty was performed. After surgery, the patient was able to return to activities of daily living. Although rare, physicians should be aware of the fact that penicillamine can cause VMH. Therefore, patients with Wilson disease should be checked regularly for changes in breast volume in order to minimize possible complications.

Keywords Wilson disease / Penicillamine / Breast disease

INTRODUCTION

Wilson disease is an autosomal recessive genetic disorder caused by the accumulation of copper within the human body. It is the most common inherited liver disease, and its symptoms may vary depending on the affected organs. In general, liver related symptoms such as fatigue, nausea and vomiting or jaundice develop in childhood whereas central nervous system related symptoms such as personality change or psychosis develop in late adulthood. Failure to excrete copper leads to various symptoms such as vomiting, weakness, itching, tremor, muscle stiffness, and psychosis, as the brain and liver are the most commonly involved organs.

Penicillamine is a metal antagonist that increases urinary copper excretion by chelation. The adverse effects of penicillamine are

known to include irreversible neurologic deficits, hypersensitivity, marrow suppression, proteinuria, and teratogenic syndrome [1]. Although rare, virginal mammary hypertrophy (VMH) induced by penicillamine has been reported [2]. In this report, we would like to share our experience of the diagnosis and treatment of penicillamine-induced VMH that developed in a patient with Wilson disease.

CASE REPORT

A 14-year-old female patient was admitted to a pediatrics department for the evaluation of elevated liver enzyme levels. After a genetic study, Wilson disease was confirmed. At that point, the patient's body mass index (BMI) was 22.14 kg/m² (height, 156.8 cm; weight, 54.5 kg). Trientine treatment was first commenced with 500 mg twice a day. Because trientine must be stored at 2°C to 8°C, the patient showed low adherence to the medication during the first month of therapy. Thus, the medication was altered to penicillamine and was continued for 8 months at a dose of 500 mg twice a day. Four months after the patient started penicillamine, breast enlargement was noticed. The medication was maintained and the patient's breasts continued to grow, which eventually resulted in difficulty with activities of daily living. The medication was then switched to 500 mg of trientine twice a day for 3 months, but the condition remained stable. At the age of 15, the patient was trans-

Received: Oct 6, 2020 Revised: Oct 16, 2020 Accepted: Oct 26, 2020
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ferred to our department for reduction mammoplasty (Fig. 1). Due to large breasts, she had difficulty in wearing clothes and suffered from neck and shoulder pain. Preoperative physical examination shows marked hypertrophy of both breasts with grade 3 breast ptosis. The patient's BMI was 22.43 kg/m² (height, 157 cm; weight, 55.3 kg). The right midclavicle to nipple distance was 36 cm, the

sternal notch to nipple distance was 37 cm, and the nipple to inframammary fold distance was 17 cm. The left midclavicle to nipple distance was 34 cm, the sternal notch to nipple distance was 35 cm, and the nipple to inframammary fold distance was 19 cm. Because both the patient and her guardians sought to minimize postoperative scarring, short-scar periareolar inferior pedicle reduction mammoplasty with a pedicle width of 8 cm was performed. The amount of excision was 974 g for the right breast and 858 g for the left breast (Fig. 2). The findings of a pathologic study were consistent with VMH (Fig. 3). Seven months after surgery, no sign of recurrence or loss of nipple sensation was noticed (Fig. 4). The patient's BMI was 20.28 kg/m² (height, 157 cm; weight, 50 kg). The patient could return to activities of daily living without difficulties.

DISCUSSION

The differential diagnosis of mammary hyperplasia in adolescents includes pregnancy, fibrocystic disease, adolescent macromastia, virginal (or juvenile) mammary hypertrophy, and other tumorous conditions such as fibroadenoma and phyllodes tumor [3].

VMH is rare and involves an atypical, alarmingly rapid growth of breast tissue during puberty. This enlargement may be unilateral or bilateral, and can occur at any time during puberty. The underlying mechanism of VMH is not clear, but drugs such as neethetazone, cyclosporine, penicillamine, and prednisolone are known to trigger the development of mammary hyperplasia [4]. Penicillamine, a chelating agent of copper, is a drug used for the treatment of Wilson disease, rheumatoid arthritis, and systemic sclerosis. The adverse effects of penicillamine include bone marrow suppression, obliterating bronchiolitis, nephritis syndrome, thyroiditis, and polyneuropathy. Breast enlargement is a rare complication, of which

Fig. 1. Preoperative photograph. Breast hypertrophy with a larger right breast was noted.

Fig. 2. Intraoperative photos. (A) Short-scar periareolar inferior pedicle reduction mammoplasty was performed. (B) The amount of excision was 974 g for the right breast and 858 g for the left breast.

Fig. 3. Histopathologic appearance of the excised left breast tissue. Proliferation of both tubular ductal structures and stromal connective tissue can be noted on hematoxylin and eosin staining (A, $\times 100$; B, $\times 200$).

Fig. 4. Photograph at 7 months after surgery.

only a few cases have been reported [5]. Because of its adverse effects, penicillamine is now considered as a second-line drug after trientine [6]. The mechanism through which penicillamine induces breast hypertrophy has not yet been clarified. It is suspected that penicillamine might alter the level of circulating prolactin or the susceptibility of mammary glands to prolactin [7]. The interval be-

tween administration of penicillamine and breast hypertrophy ranges from 12 weeks to 18 months [2].

Because of rapid breast growth, VMH patients usually present with neck pain, shoulder pain, or back pain [8]. Skin irritation or intertrigo are also frequently seen along brassiere straps. Furthermore, patients suffer from significant emotional stress, which can result in dissatisfaction with their body image and poor self-esteem. Since Wilson disease is usually diagnosed in childhood or early adolescence, this could pose a critical issue.

Because of the rarity of the disease, there is no evidence-based treatment protocol for drug-induced VMH. One study reported that discontinuation of penicillamine and administration of danazol resulted in regression of breast hypertrophy [9]. Attempts to control breast growth through hormonal agents including bromocriptine, medroxyprogesterone, and tamoxifen have been tried, but the results were inconsistent [10]. If medical treatment is unsuccessful, reduction mammoplasty can be considered. Although breast reduction is an effective and relatively safe procedure, both the patient and her guardians should be involved in the decision-making process. Detailed information regarding the operation should be provided prior to surgery. If the patient is not motivated, caution is needed not to hasten the procedure.

Reduction mammoplasty can produce immediate relief of physical symptoms and psychological improvements. However, the risk of loss of nipple sensation and inability to carry out breastfeeding should be addressed prior to surgery. A previous study has shown that the success rate of breastfeeding after reduction mammoplasty is not significantly different depending the type of pedicle (62%, 65%, and 64% for superior, medial, and inferior pedicle techniques, respectively) [11]. Only 2% of patients report impaired or complete loss of nipple sensation after reduction mammoplasty.

Because the breasts naturally grow during puberty, adolescent patients with Wilson disease may not perceive the adverse effect of penicillamine. For this reason, a close observation of breast volume is required for physicians treating patients with penicillamine. In addition, surgeons should consider breast reduction for patients with VMH suffering from physical and emotional distress.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study was exempted from ethical approval (exemption approval No. HC20ZASI0211).

Patient consent

The patient provided written informed consent for the publication and the use of her images.

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