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Cortisone-induced gigantomastia during chemotherapy

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SUMMARY: **Cortisone-induced gigantomastia during chemotherapy.**

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Gigantomastia is a rare, psychologically and physically disabling condition characterized by excessive breast growth. There is no universal consensus on the definition of gigantomastia, but it is most commonly described as breast enlargement that requires removal ranging from 800 to 2000 g, or even a D cup bra size. It typically occurs in the setting of marked hormonal changes such as puberty and pregnancy; however, there have also been a number of reports of gigantomastia in the setting of autoimmune diseases.

Rare association of gigantomastia included medicinal aetiologies such as penicillamine, neothetazone, and cyclosporine. The mechanism of action of these pharmacological agents remains unclear.

We report the first case of gigantomastia associated with cortisone in the setting of ovary cancer treated with chemotherapy cycles after hysterectomy and bilateral adnexectomy. Moreover, we propose a clinic evidence and a metabolic theory to explain this association.

RIASSUNTO: **Gigantomastia indotta da cortisone durante chemioterapia.**

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La gigantomastia è una rara condizione caratterizzata da un eccessiva crescita della mammella, disabilitante sia sul piano psicologico che fisico. Non c'è consenso universale sulla definizione di gigantomastia, ma i più la descrivono come una crescita abnorme della mammella tale da richiedere la rimozione tra 800 e 2000 g di tessuto o l'equivalente di una coppa D di reggiseno. Essa insorge tipicamente durante la pubertà o la gravidanza quando si verificano importanti cambiamenti ormonali; inoltre, sono stati riportati casi di gigantomastia nell'ambito di patologie autoimmuni.

Una rara associazione con la gigantomastia include le forme ad eziologia farmacologica da penicillamina, neothetazone e ciclosporina. Il meccanismo d'azione di questi farmaci rimane sconosciuto.

Riportiamo il primo caso di gigantomastia associato a terapia cortisonica in una paziente con tumore dell'ovaio trattata con cicli di chemioterapia dopo isterectomia e annessectomia bilaterale. Inoltre, proponiamo un'evidenza clinica e una teoria metabolica per spiegare tale associazione.

KEY WORDS: Gigantomastia - Breast hypertrophy - Ovary cancer - Cortisone therapy - Chemotherapy
Gigantomastia - Ipertrofia mammaria - Tumore dell'ovaio - Terapia cortisonica - Chemioterapia.

Introduction

Gigantomastia is a rare breast condition characterized by excessive, rapid and diffuse breast hypertrophy that can be physically and psychosocially disabling for the patient. There is no universal consensus on the definition of this pathology, many authors cite gigantomastia as breast enlargement that requires reduction of over 1.500 g per breast. However there is discordance in the literature with the weight of reduction ranging from 800 to 2.000 g, or even a D cup bra size (1-4).

Symptoms include mastalgia, local ulceration/infection, postural problems, back pain and chronic traction injury to $4^{th}/5^{th}/6^{th}$ intercostal nerves with resultant loss of nipple sensation. Complication are thought to be mostly secondary to the tension on the skin from increased breast weight. Skin changes of the breast have also been documented and include skin atrophy, hyperaemia, marked venous engorgement, cellulitis, ulceration, necrosis and dilation of the nipple-areola complex (1, 4).

It is typically associated with hormonal changes such as gravid/gestional gigantomastia or pubertal–indu-

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ced/juvenile gigantomastia, there have also been a number of reports of gigantomastia in the setting of autoimmune diseases (5-8).

It is rare for breast hypertrophy to be induced by drugs. In particular in literature, gigantomastia has been reported to be associated by only three drugs: penicillamine, neothetazone and cyclosporine (9-11).

We report the first case of gigantomastia associated with cortisone therapy in the setting of ovarian cancer treated with Taxol, Platin and Soldesam after hysterectomy and bilateral adnexectomy.

Case report

In December 2006, a 47 year-old women presented to Department of Dermatology and Plastic and Reconstructive Surgery of the "Sapienza" University of Rome with a two-year history of excessive breast growth.

Her medical history is notable for ovarian cystoadenocarcinoma. In November 2006 the patient underwent hysterectomy and bilateral adnexectomy. After the surgery the patient underwent 6 cycles of adjuvant chemotherapy with Platin (648 mg), Taxolo (283 mg) and Soldesam (4 mg, two times die for 4 dies after each chemotherapy administration). Within 2 months of starting chemotherapy, breast enlargement was noted. Her breasts were tender and swollen, her ring size increased from 5 to 8 and her weight from 56 to 65 kg. Moreover she referred postural problem and cervical pain. The workup included mammography an serological analysis. The mammogram revealed 50% fat and 50% fibroglandular tissue without any masses or abnormalities, so a diagnosis of macromastia was made.

Laboratory studies revealed elevated erythrocyte sedimentation rate, glycemia, ALT, LDL, total cholesterol and triglycerides.

Clinical examination showed an apparently healthy woman with firm, pendulous, and edematous breasts. There was "peau d'orange" texturing on the underside of both breasts that were consistent with lymphoedema. The left breast was significantly larger than the right. The G-C distance was measured at 34 cm on the right and 32 cm on the left. The E-C distance was 34 cm on the right and 33 on the left. The nipple diameter (D-D') was 6,5 cm on the left and 6 cm on the right. The distance A- S was 16 cm on the left and 15 cm on the right (Fig. 1).

In December 2006, a bilateral breast reduction and nipple grafting was perfomed with Torek's technique whereby 950 gr e 1.150 gr of tissue was removed from the right and left breast, respectively. Histological examination revealed an increase in fibrosis and duct dilatation , but no malignancy.

In December 2008 the patient underwent bilateral paraortic and pelvic lymphadenectomy for ovarian cancer metastasis. After surgery the patient underwent a further 6 cycles of chemotheraphy with Carboplatin AUC 5 Paclitaxel® (175 mg/m^2) but no cortisone therapy. The patient after therapy had no collateral effects like mammary hypertrophy, wheight increase or alteration of laboratory parameters.

At the time of this report, the patient has not had any recurrence of breast hypertrophy during three postoperative years.

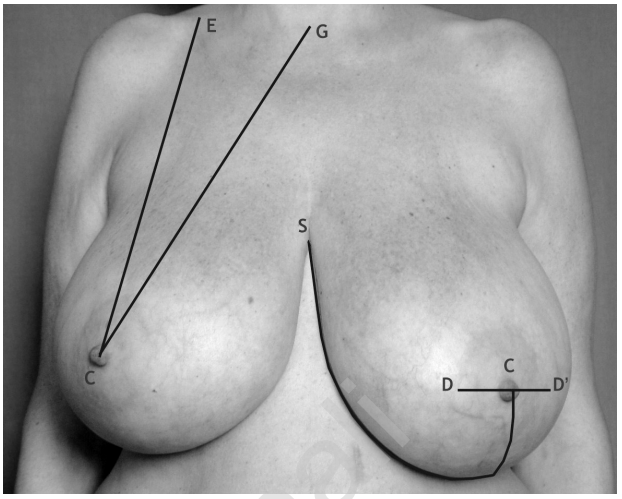

Fig. 1 - Preoperative view of a 47-year-old woman with bilateral gigantomastia. (C nipple, DD nipple diameter, E clavicular region, G jugular region, S mammary fold).

Discussion

Gigantomastia is sometimes observed at puberty or during pregnancy (12-14). The precise aetiology remains unknown; however, many mechanisms have been implicated including hormonal abnormalities, hormone receptor hypersensivity, malignancy, drug induction, genetics, and autoimmunity (1, 3, 15).

Rare associations of gigantomastia include medicinal aetiologies. In 1970, drug-induced gigantomastia was reported for the first time by Scot (10). It was induced by the antibiotic Neothetazone. In 1973, Desai (16) first described that breast hypertrophy could be induced by D- penicillamine. Another drug that was associated in literature with gigantomastia was cyclosporine (11).

We report the first case of the association between gigantomastia and cortisone drugs. The cause of this association is unknown but we propose both clinic evidence and a metabolic theory to explain this association.

The clinic evidence is that the patient developed a rapid and excessive breast augmentation and an increase of weight (10 kg) after hysterectomy and bilateral adnexectomy surgery followed by chemotherapy. The drugs administrated in the first chemotherapy cycle were Taxol, Platin with the addition of desametasone (Soldesam) to reduce the collateral effects of the therapy like nausea and vomit. In December 2006, the patient underwent bilateral breast reduction surgery. After two years she was diagnosed as having lymph nodes metastasis and pelvic and paraortic bilateral linfadenectomy was performed. Following surgery she underwent a new chemotherapy cycle without cortisone therapy. In this case she was not subject to breast enlargement or weight gain. According to clinical history we can underline that the difference between the first and second chemotherapy treatment was in the utilisation of desametasone. Furthermore, the drugs Taxol, Platin, Paclitaxel and Carboplatin acts as inhibitors which reduce cellular proli-

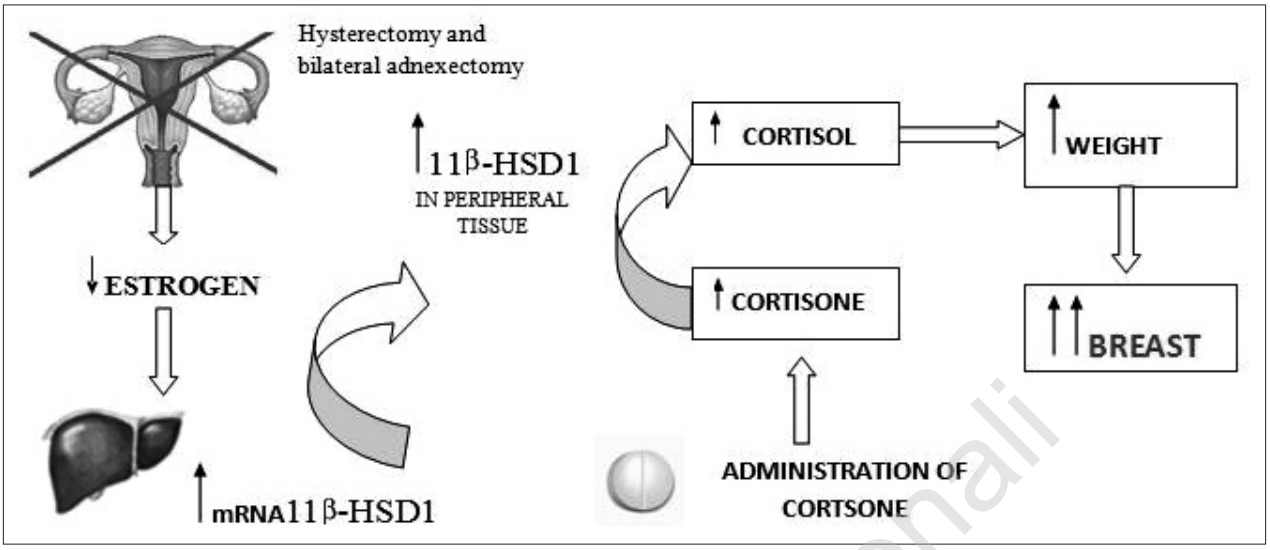

Fig. 2 - Metabolic theory.

feration, and as such it is unlikely that they would induce gigantomastia.

The metabolic theory is in the role of glucorticoids and effects of estrogen reduction after hysterectomy. Glucorticoids are important regulators of adipose tissue metabolism and fat distribution (17). Recent studies suggest that peripheral cortisol production is increased in obesity (18, 19). Local tissue regulation of glucorticoid action is primarily determined by the β-hydroxysteroid dehydrogenases (11β-HSDs) that interconvert hormonally active cortisol and inert cortisone. This enzyme is known to play a significant role in the normal hypothalamus-pituitary-adrenal (HPA) axis, and it is implicated in metabolic syndrome. It has also been found, in a recent study, that estrogen completely repress hepatic and renal 11β-HSD mRNA expression and activity in rodents (20, 21), so reducing cortisol action. In the ovariectomy rats studies have revealed an up-regulation of 11β-HSD1. In other studies of transgenic mice it has been shown that its increased expression in adipose tissue is associated with the development of the metabolic syndrome (22, 23), and conversely that improved inactivation of glucorticoid in adipocytes protects against metabolic syndrome (24), that was most likely due to changes in tissue adipose body composition. In a study by Soren et al. (17) they found that estrogen deficiency induced by ovariectomy in rats resulted in approximate fourfold increase in adypose 11β-HSD1 mRNA. This up-regulation was reversed by estrogen treatment, indicating that it might be a result of estrogen deficiency. In conclusion, estrogen deficiency induced by ovariectomy results in an excessive increase in 11β-HSD1gene expression and an augmentation of body weight in rats.

If we apply this theory in our patient the bilater adnexectomy could determine a reduction of estrogen resulting in an increase of 11β-HSD1 expression and activity associated with administration of cortisone drugs, could determine an increase in tissue cortisol with a resulting gain in weight and subsequent breast enlargement.

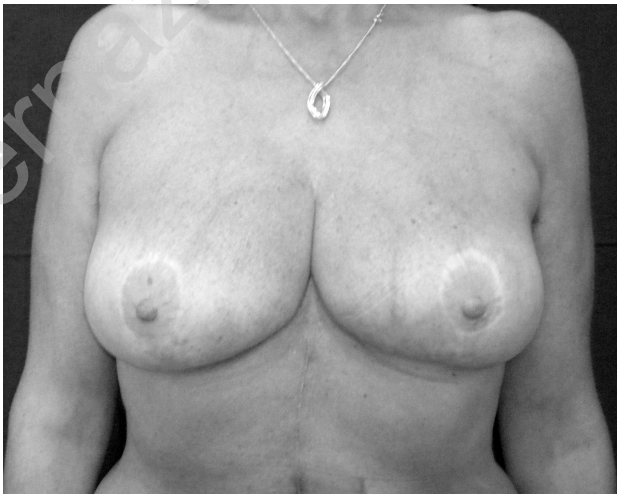

Fig. 3 - Postoperative view.

Moreover in our patient we noticed an increase of the glycemia that may be explained by increased glucorticoid activity, that, in turn, may induce insulin resistance.

Conclusion

Only a few cases of gigantomastia induced by drugs are described in literature. In all these cases the precise

aetiology and pathogenesis remain unclear.

Considering the clinic history of the patient and the effects of the administered drugs, we believe that the pharmacological effect of the drugs could be responsible for the difference in breast augmentation and weight gain, between the first chemotheraphy with cortisone and the second one cycle. Besides, ovariectomy results in estrogen reduction and subsequently augmentation of mRNA 11β-HSD1 with cortisol elevation. In fact, as reported in metabolic syndrome the increase of glucorticoids activity results in the augmentation of adipose tissue and weight gain. Moreover, in literature the association between gigantomastia and autoimmune syndromes, such as systemic lupus erythematosus, with a cortisone-based therapy, has been described. These findings strongly support our hypothesis.

In conclusion, in ovariectomy patients we suggests paying particular attention to the analysis of the metabolic parameters and a close monitoring of any cortisone therapy.

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