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, 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 clinical evidence and a metabolic theory to explain this association.

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.

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KEY WORDS: Gigantomastia - Breast hypertrophy - Ovary cancer - Cortisone therapy - Chemotherapy

Gigantomastia - Ipertrofia mammaria - Tumore dell’ovaio - Terapia cortisonica - Chemioterapia.

Cortisone-induced gigantomastia during chemotherapy

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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 è esistito un 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.

RIASSUNTO: Gigantomastia indotta da cortisone durante chemioterapia.

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Gigantomastia - Ipertrofia mammaria - Tumore dell’ovaio - Terapia cortisonica - Chemioterapia.
Corticosterone-induced gigantomastia during chemotherapy

In December 2006, a 47-year-old woman 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), Taxol (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 and serological analysis. The mammogram revealed 50% fat and 50% fibroglandular tissue without any masses or abnormalities, so a diagnosis of macroamastia 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 32 cm on the right and 32 cm on the left. The E-C distance was 34 cm on the right and 33 cm on the left. The nipple diameter (D-D') was 6,5 cm on the left and 6 cm on the right. The A-S was 15 cm on the left and 15 cm on the right (Fig. 1).

In December 2006, a bilateral breast reduction and nipple grafting was performed with Toekik's technique whereby 950 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 paraaortic and pelvic lymphadenectomy for ovarian cancer metastasis. After surgery the patient underwent a further 6 cycles of chemotherapy with Carboplatin AUC 5 Paclitaxel (175 mg/m²) but no cortisone therapy. The patient after therapy had no collateral effects like mammary hypertrophy, weight 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.

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 hypersensitivity, malignancy, drug induction, genetics, and autoimmunity (1, 3, 15).

Rare associations of gigantomastia include medicinal aetologies. 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 paraaortic bilateral lymphadenectomy 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-
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 glucocorticoid 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 cortisone 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 glucocorticoid 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 adipose 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-HSD1 expression and an augmentation of body weight in rats.

If we apply this theory in our patient the bilateral 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.

Moreover in our patient we noticed an increase of the glycemia that may be explained by increased glucocorticoid 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
Cortisone-induced gigantomastia during chemotherapy

Aetiology and pathogenesis remain unclear. Considering the clinical 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 chemotherapy 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 glucocorticoids 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 suggest paying particular attention to the analysis of the metabolic parameters and a close monitoring of any cortisone therapy.

References