

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 4th/5th/6th intercostal nerves with resultant loss of nipple sensation. Complications 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/gestational 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 cystadenocarcinoma. 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 performed 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 chemotherapy with Carboplatin AUC 5 Paclitaxel® (175 mg/m²) 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.

Discussion

Gigantomastia is sometimes observed at puberty or during pregnancy (12-14). The precise aetiology remains

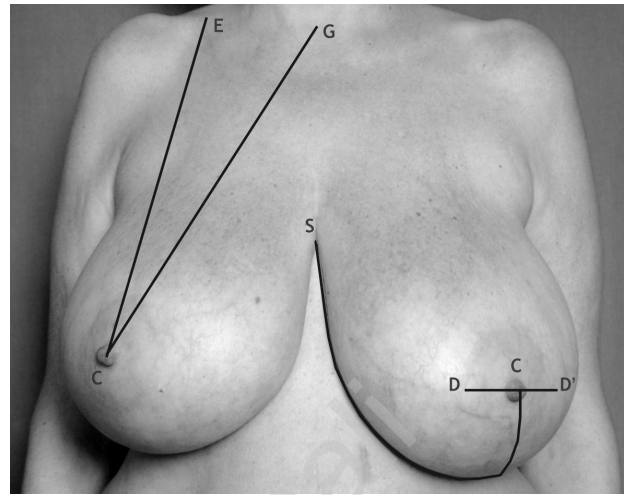


Fig. 1 - Preoperative view of a 47-year-old woman with bilateral gigantomastia. (C nipple, DD nipple diameter, E clavicular region, G jugular region, S mammary fold).

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 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-

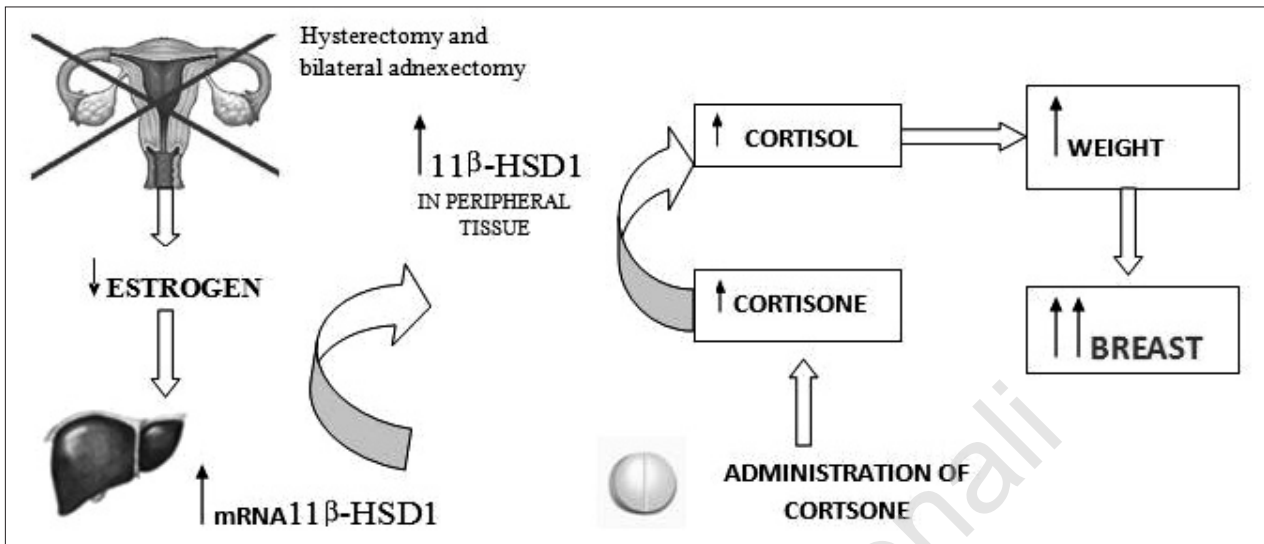


Fig. 2 - Metabolic theory.

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 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 gene expression and an augmentation of body weight in rats.

If we apply this theory in our patient the bilateral ad-

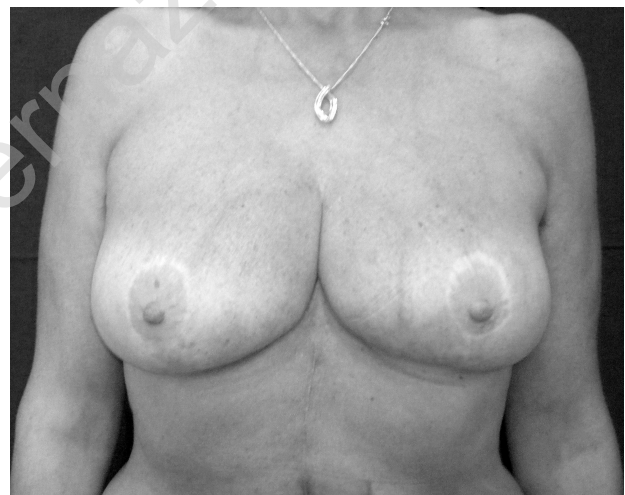


Fig. 3 - Postoperative view.

nexectomy 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 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 chemotherapy with cortisone and the second one cycle. Besides, ovariectomy results in estrogen reduction and subsequently augmentation of mRNA 11 β -HSD1 with cortisol elevation. In fact, as reported in metabolic syndrome the increase of glucorticoids ac-

tivity 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

1. Dancey A, Khan M, Dawson J, Peart F. Gigantomastia- a classification and review of the literature. *J Plas Reconstr Aesthet Surg* 2008;61:493-502.
2. Antevsky BM, Smilevsky DA, Stojovsky MZ, Filipovsky VA, Banev SG. Extreme gigantomastia in pregnancy: a case report and review of literature. *Arch Gynecol Obstet* 2007; 275:149-153.
3. Swelstad MR, Swelstad BB, Rao VK, Gutowsky KA. Management of gestational gigantomastia. *Plast Reconstr Surg* 2006;118:840-848.
4. Le EN, McGirt LY, Abuav R. Gigantomastia and autoimmunity: a case report. *Lupus*(2009);181015-1018.
5. Shelley WB, Hurlley HJ. An unusual autoimmune syndrome. Erythema annulare centrifugum, generalized pigmentation and breast hypertrophy. *Arch Dermatol* 1960;81:889-897.
6. Shelley WB. An unusual auto-immune syndrome. A follow-up with reference to breast hypertrophy, systemic lupus erythematosus and verrucae. *Acta Derm Venereol* 1972;52:33-37.
7. Duffy DA, Demers ML, Molin MR. Systemic lupus erythematosus with breast gigantism. *J Rheumatol* 1995;22:1214-1215.
8. Propper DJ, Reid DM, Stankler L, Eastmond CJ. Breast vasculitis in association with breast gigantism in a pregnant patient with systemic lupus erythematosus. *Ann Reum Dis* 1991;50:577-578.
9. Sakay Y, Wakamatsu S, Ono K, et al. Gigantomastia induced by bucillamine. *Ann Plast Surg* 2002;49:193-5.
10. Scott EHM. Hypertrophy of the breast, possibly related to medication: a case report. *South Afr Med J* 1970;44:449-50.
11. Cerveli V, Orlando G, Giucideandre F. Gigantomastia and breast lumps in a kidney transplant recipient. *Transplantation Proc* 1999;31:3224-5.
12. Hasegawa T, Satoh M, Kaneko F. Giant bilateral macromastia: a case report. *Jpn J Plast Surg* 1994;37:605-609.
13. Fisher W, Smith JW. Macromastia during puberty. *Plast Reconstr Surg* 1971;41:445-451.
14. Kupfer D, Dingman D, Broadbent R. Juvenile breast hypertrophy: report of a familiar pattern and review of the literature. *Plast Reconstr Surg* 1992;90:303-309.
15. Gowrin-Yehudain J, Kogan L, Cohen HI, Falik-Zakkai TC. Familial juvenile hypertrophy of the breast. *J Adolesc Health* 2004;35:151-155.
16. Desai SN. Sudden gigantism of breasts: drug induced? *Br J Plast Surg* 1973;26:371-372.
17. Paulsen SK, Nielsen MP, Richelsen B, Bruun JM, Flyvbjerg A, Pedersen SB. Obesity (Silver Spring). 2008 Apr;16(4):731-5.
18. Seckl JR, Morton NM, Chapman KE, Walker BR. Glucocorticoids and 11 β -hydroxysteroid dehydrogenase in adipose tissue. *Recent Prog Horm Res* 2004;59:359-393.
19. Stewart PM, Boulton A, Kumar S, Clark PM, Shackleton CH. Cortisol metabolism in human obesity: impaired cortisone cortisol conversion in subjects with central adiposity. *J Clin Endocrinol Metab* 1999;84:1022-1027.
20. Jamieson PM, Nyirenda MJ, Walker BR, Chapman KE, Seckl JR. Interactions between oestradiol and glucocorticoid regulatory effects on liver-specific glucocorticoid-inducible genes: possible evidence for a role of hepatic 11 β -hydroxysteroid dehydrogenase type 1. *J Endocrinol* 1999;160:103-109.
21. Low SC, Assaad SN, Rajan V, Chapman KE, Edwards CR, Seckl JR. Regulation of 11 β -hydroxysteroid dehydrogenase by sex steroids in vivo: further evidence for the existence of a second dehydrogenase in rat kidney. *J Endocrinol* 1993;139:27-35.
22. Masuzaki H, Yamamoto H, Kenyon CJ et al. Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. *J Clin Invest* 2003;112:83-90.
23. Masuzaki H, Paterson J, Shinyama H et al. A transgenic model of visceral obesity and the metabolic syndrome. *Science* 2001;294:2166-2170.
24. Kershaw EE, Morton NM, Dhillon H, Ramage L, Seckl JR, Flier JS. Adipocyte-specific glucocorticoid inactivation protects against diet-induced obesity. *Diabetes* 2005;54:1023-1031.