Case report

# Gynecomastia disclosing diagnosis of Leydig cell tumour in a man with thalassemia, secondary hypogonadism and testis microlithiasis

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**Abstract.** Aim of this paper is to report about a 35-year old man suffering from β-Thalassemia major and longstanding untreated hypogonadotropic hypogonadism, who was referred because of a recent onset and painful bilateral gynecomastia, with no palpable testicular masses. Due to the finding of a solid mass at left testis ultrasonography, monolateral testicular exeresis was performed and histology revealed a Leydig Cell Tumour and testicular microlithiasis. Post-surgical restoration of testosterone/estradiol ratio under testosterone therapy was followed by a very rapid reduction of gynecomastia. Our report confirms the usefulness of scrotal ultrasonography for finding an occult testicular tumour in a patient with painful and recent onset bilateral gynecomastia and underlines: a) the important role of testosterone/estradiol ratio in the pathophysiology of gynecomastia; b) the questionable significance of testicular microlithiasis as marker of testis tumours; c) the possible association between β-Thalassemia and tumoral pathologies. (www.actabiomedica.it)

**Key words:** Gynecomastia, hypogonadotropic hypogonadism, Leydig cell tumour, testicular microlithiasis, thalassemia

## Introduction

Gynecomastia is a common clinical finding due to benign proliferation of the male breast glandular component. Gynecomastia may have common physiological causes or be drug-induced, but it may also be related to various pathologies, such as testicular tumours, which are seen in 3% of men with gynecomastia (1). Irrespective of the aetiology, the pathophysiological mechanisms of gynecomastia are primarily based on reduced testosterone (T)/estradiol (E2) ratio.

Aim of this paper is to report about a 35-year old man suffering from both β-Thalassemia major and longstanding untreated hypogonadotropic hypogonadism (HH), who was referred to our attention because of a 6- month history of painful bilateral breast enlargement.

## Case report

Our patient required repeated blood transfusion (from the age of 4 year) and chelation therapy (from the age of 11 year) but the execution of them emerged non optimal and irregular. At the age of 16, on the light of no signs of spontaneous pubertal development and hormonal evaluation (LH-RH stimulation test was not able to elicit any significant increase of both FSH: peak 0.1 mIU ml-1 and LH: peak 0.2 mIU ml-1) the diagnosis of HH related to β-Thalassemia was performed. The replacement therapy with T enanthate was proposed but refused by the patient. No other evident endocrinopathies have been detected.

Anamnestic evaluation was unremarkable for other disease antecedents and/or the use of drugs that are known to be possibly involved in the aetiology of

gynecomastia. Family history too was unremarkable. At the time of the first evaluation physical examination revealed no secretion from the nipples, no signs of spontaneous pubertal development and/or peripheral androgenization. Testicular volume was bilaterally reduced with respect to age (4 ml) and no masses were palpable. Endocrine evaluations confirmed a picture of HH, with prepubertal baseline levels of FSH, LH and T (Table 1) and T/E2 was therefore reduced (6.8). Left testis ultrasonography (US) evidenced a ill-defined, solid and heterogeneous mass, containing multiple nonshadowing hyperechoic areas (Figure 1), whereas multiple punctuate echogenic foci were seen in both testes. The mammary US revealed the hypertrophy of the gland without any focal damage.

Tumoral markers α-fetoprotein, LDH and β-HCG were negative.

Owing to the absence of erections and ejaculations, semen analysis was not performed.

On the advice of urologist, the patient underwent surgical exeresis of left testis. Histological analysis showed a well- capsulated tumour characterized by typical Leydig cells with eosinophilic cytoplasm, round nuclei and evident nucleoli, together with a diffuse picture of seminiferous cord aplasia. A picture of testicular microlithiasis (TM) with intra-tubular microcalcifications was also documented at histology.

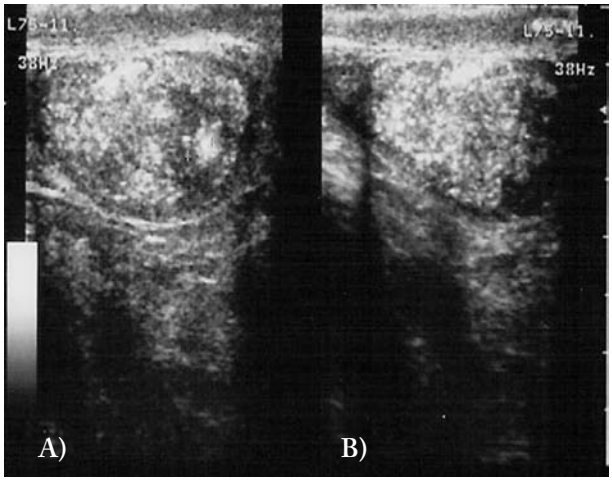


**Figure 1**. Longitudinal US image of left testis showing a heterogeneous mass that includes multiple nonshadowing echogenic areas (A); multiple punctuate echogenic foci are also diffusely scattered in the testis (B)

**Table 1.** The basal levels of total T, E2, FSH, LH, free T4, TSH before the start of replacement therapy of T enanthate - at the diagnosis of testicular tumour (A) and after 4 months of replacement therapy with T enanthate (B)

| | A | B | Normal range |
|---|---|---|---|
| FSH (mIU ml-1) | 0.02 | 0.1 | 1.4-5.8 |
| LH (mIU ml-1) | 0.1 | 0.1 | 1.5-9.3 |
| T (ng ml-1) | 0.39 | 4.3 | 2.8-8.0 |
| E2 (pg ml-1) | 5.7 | 29.6 | 0-41.2 |
| Free T4 (ng dl-1) | 1.22 | 1.4 | 0.89-1.76 |
| TSH (mIU ml-1) | 2.2 | 2.8 | 0.35-5.5 |

After surgery, due to the pre-existing condition of HH, our patient underwent replacement therapy with T enanthate (250 mg monthly), that had been always refused until then. Under this substitutive treatment circulating T levels normalized (Table 1) and consequently T/E2 ratio increased from 6.8 to 14.5. Four months later gynecomastia was found to be significantly reduced on both clinical and US evaluation.

## Discussion

In this patient a painful and recent onset bilateral gynecomastia was the key manifestation that disclosed preclinical diagnosis of a Leydig Cell Tumour (LCT). It is well known that not all testicular tumours are palpable and that gynecomastia may be the first presenting, and often forgotten, sign of a palpable or impalpable testicular tumour (2). Therefore it has been very recently recommended to screen by scrotal US all the high-risk patients, i.e. the young adults with rapid onset bilateral ginecomastia (3). According to another recent report LCTs represent a frequent cause of gynecomastia (12.5%) and scrotal US has been suggested to be performed in all the males with gynecomastia (4).

In the present case the risk of LCTs was furtherly enhanced by the coexistence of longstanding untreated HH, that is known to be a significant risk factor for the development of testicular tumours (5). HH in our patient was related to β-Thalassemia and was caused by haemosiderosis produced by repeated blood transfusions with not optimal chelation therapy. Whether the occurrence of LCT in thalassemic pa-

tient is the result of longstanding untreated HH or just a pure coincidence is not known. Moreover the carcinogenic effect of iron or deferoxamine has been taken in consideration in the development of malignancies in thalassemic patients (6). Our report confirms the usefulness of scrotal US for finding an occult testicular tumour in a patient with recent onset gynecomastia (2) and underlines also the important role played by T/E2 ratio in the pathophysiology of gynecomastia. In our case, in fact, surgical exeresis of the causative interstitial tumour and the concomitant onset of testosterone therapy with consequent restoration of T/E2 ratio were followed by a very rapid regression of gynecomastia.

Patients with LCT-induced breast enlargement are known to usually undergo a slow resolution of gynecomastia, due to post-surgical normalization of estrogen levels (7). In the present case the restoration of T/E2 ratio and the consequent resolution of gynecomastia were very rapid, probably owing to the concomitant onset of testosterone replacement treatment. In our patient testosterone therapy was necessary because of the association with HH, that is a well-known complication of β-Thalassemia (8).

In this case the finding of LCT was associated with testicular microlithiasis (TM), an imaging entity with questionable significance as a marker of testicular tumours (9). According to a recent follow-up study, this US finding does not have any predictive value for the development over time of a testicular tumour and therefore it was concluded that an intensive screening program for men with TM is not cost-effective (10). Although there is no strong evidence to suggest that TM is to be considered as a premalignant lesion by itself (10), nevertheless an association between TM and cancer exists (9). Therefore in the patients with TM and no other associated risk factors, a testicular self examination, however, is probably to be suggested.

Finally, this report raises another important concern regarding the possible association between β-Thalassemia and tumoral pathologies. This point has been recently developed by Benetatos et al (11), who reported some cases with this association. Interestingly in that report one of the associated tumours was a seminoma. Those Authors concluded that the occurrence of tumours in thalassemic patients is an emerging concern for physicians. However, whether there is a link between thalassemia and tumours or whether tumours are more frequent in thalassemic patients simply because today they live longer, is still to be defined (11).

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