Unilateral breast enlargement in males during adolescence (10-19 years): review of current literature and personal experience

Vincenzo De Sanctis[1], Ashraf T Soliman[2], Ploutarchos Tzoulis[3], Shahina Daar[4], Salvatore Di Maio[5], Christos Kattamis[6]

[1]Coordinator of ICET-A Network (International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine) and Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; [2]Department of Pediatrics, Division of Endocrinology, Hamad General Hospital, Doha, Qatar; [3]Department of Diabetes and Endocrinology, Whittington Hospital, University College London, London, UK; [4]Department of Haematology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Sultanate of Oman & Stellenbosch Institute for Advanced Study, Wallenberg Research Centre at Stellenbosch University, Stellenbosch, South Africa; [5]Emeritus Director in Pediatrics, Children's Hospital "Santobono-Pausilipon", Naples, Italy; [6]Thalassemia Unit, First Department of Paediatrics, National Kapodistrian University of Athens, Greece

Abstract. Idiopathic unilateral breast enlargement (UBE) in males is a, commonly overlooked, diagnosis of exclusion that requires careful history, meticulous physical examination, and pertinent laboratory studies to exclude the possible pathologic causes. The aims of the present update are to review the current literature on UBE in subjects during adolescent age (10-19 years) in 18 cases, and to report the personal experience in 13 adolescents referred to our unit during the last four decades. In total, our survey and personal experience include 31 UBE cases, 10 of whom (32.2%) being idiopathic or familial gynecomastia (GM). In 3/31 (9.6%) UBE was due to breast sarcoma/ carcinoma; one patient (11-years old) had a 5-year history of painless lump in the right breast, which increased gradually in size followed by bloody nipple discharge. In the personal cases of 13 adolescents, a moderate to marked UBE was secondary to: treatment with androgens (2 β-thalassemic patients with hypogonadism), high estrogen/androgen ratio in 2 Klinefelter syndrome patients, peripheral aromatization of androgens in 1 patient with non-classical 21-hydroxylase deficiency (NC-21-OH-D). One patient had subareolar hematoma due to injury. In 2 patients (15,3%) marked UBE was due to cystic lymphangioma (histologically proved). Furthermore, 5 patients were characterized as idiopathic UBE In clinical practice, the persistence of UBE for long period before diagnosis necessitates attention and further evaluation. Underlying causes should be treated, when possible, while surgery can be offered to patients with persistent or atypical signs and/or symptoms of UBE. For the optimal management of this condition, better collaboration between primary care physician and specialists is mandatory. (www.actabiomedica.it)

Key words: Unilateral breast enlargement, adolescence, gynecomastia, revision of literature, personal experience, cystic lymphangioma

Introduction

Gynecomastia (GM) refers to an enlargement of the male breast caused by a benign proliferation of the glandular tissue (1). GM may have physiological (newborn, pubertal, senile) or pathological etiology and may be unilateral or bilateral. Clinical manifestations consist of a soft, elastic, nodule-like retroareolar mass that is occasionally associated with pain. The overlying skin is intact and resembles that of adjacent areas.

The most common differential diagnoses of GM are pseudogynecomastia (pseudo-GM) and malignancy. Pseudo-GM refers to breast enlargement (usually bilaterally) not due to glandular proliferation and more frequently caused by an excess of adipose tissue. Pseudo-GM is not necessarily associated with obesity (2). It maybe observed in subjects with lipoma, neurofibromatosis, lymphangioma and hematoma secondary to trauma. The diagnosis of pseudo-GM due to overweight and obesity is based mainly on clinical examination.

In contrast to pubertal bilateral GM, studies on unilateral GM or unilateral breast enlargement (UBE) in adolescents received less attention with only few cases reported in the medical literature. UBE is a diagnosis of exclusion that requires careful history, meticulous physical examination, and pertinent laboratory studies to exclude any possible pathologic cause.Thus, there is lack of data on its etiology, as well as diagnostic and therapeutic approaches.

Prevalence of GM

The prevalence of GM in adolescent males varies widely depending on the cohorts of subjects studied, the specific imaging modality, and the diagnostic criteria applied (2). Different investigators have defined GM as a palpable mass of subareolar breast tissue measuring from 0.5, to 2 cm (3,4). A study of 506 adolescent and adult males presenting to emergency departments with trauma who underwent a chest computed tomography (CT) scan showed that some breast glandular tissues in males is a normal finding with 90^{th}, 95^{th}, and 97.5^{th} percentiles of normal breast tissue being 2.2, 2.6, and 3.6 cm, respectively (5).

These parameters are important when comparing the criteria used by different investigators to define GM prevalence. GM may be an incidental finding on routine physical examination or may appear as new-onset palpable breast mass with or without mastalgia. GM can be detected when the size of the glandular tissue exceeds 0.5 cm in diameter. It is generally considered significant when there is ≥2 cm of palpable breast tissue.

In the largest cross-sectional study performed to date on GM in adolescents, the prevalence was found to be 4% in males aged 10 to 19 years. The prevalence of bilateral GM was 64.5% and unilateral 35.5%. The presence of GM was defined as a firm palpable button of subareolar breast tissue at least 1 cm in diameter (4).

The pathophysiology of GM includes a wide spectrum of factors: physiological, endocrinological, metabolic, neoplastic, medication- and illicit drugs-induced (1).

Physiology and pathology of GM

Physiological GM has three major peaks across the male life course: neonatal period, puberty, and advanced adult age with the highest prevalence in senility (1). Pubertal GM may present as early as the age of 10 years, with a peak onset between the ages of 13 and 14 years, followed by a decline in late teenage. During puberty, GM can develop because of hormonal instability caused by imbalances between blood levels of testosterone and estrogens. Clinically, it consists of a nodule-like retroareolar mass. The overlying skin is intact and resembles that of adjacent areas. GM of recent onset may be associated with pain or tenderness (mastodynia) (3,4). Untreated pubertal GM regresses substantially or resolves in >70 % of adolescents after one year (6-9), although regression may take up to two years in some patients. After this period, it is unlikely to regress substantially, either spontaneously or with medical therapy, because of the presence of fibrosis (4, 6-9).

The three characteristic patterns related to pubertal GM are nodular, dendritic and and diffuse glandular. The nodular form is characterized by prominent ductal hyperplasia and cellular/ proliferative stroma. Generally, it is the sign of the early (florid) phase corresponding to a duration of less than 1 year. When GM becomes long-standing, dilated ducts with periductal fibrosis and stromal hyalinization are seen on histological examination (fibrous stage) (10-12), and usually appears on ultrasonography (US) as a hypoechoic lesion with irregular or macrolobulated margins (dendritic form). It is irreversible due to chronic changes and fibrosis. The diffuse pattern may display a combination

of findings of nodular and dendritic GM, and is often linked to the use of exogenous hormones (13).

GM may be due to diverse pathological conditions. The differential diagnosis includes: an increase in the circulating and/or local breast tissue ratio of estrogens to androgens, excessive aromatization of testosterone and other androgens to estrogens, steroid displacement from sex-hormone binding-globulin (SHBG), which binds androgens more avidly than estrogen, resulting in a higher estrogen to testosterone ratio (14,15) and malignancy (1,14-16).

Aims of current update

The present update aims to review the current literature on UBE in boys, aged 10-19 years, and to report the personal experience in adolescents during the last four decades.

Material and methods

(a) Literature review

PubMed and Google Scholar databases were reviewed from 1957 to December of 2022. The following search terms were used: "children/adolescents AND unilateral GM", "adolescents AND unilateral breast enlargement", " adolescent males AND breast mass ", "breast disorders AND male adolescents", " adolescents AND atypical GM", "unilateral breast enlargement AND differential diagnosis". Search results were then screened for relevance based on the title and abstract, and in cases of uncertain relevance, the entire article was reviewed.

All relevant articles were reviewed for clinical and pathological findings. Applicable references were also checked for inclusion in this review. The initial literature search yielded 236 articles in total; however, after titles and abstracts were screened for relevance, only reports in adolescents with unilateral GM were reviewed for clinical and diagnostic characteristics, and final diagnosis.

According to WHO (17), adolescence is considered the phase of life between childhood and adulthood (from 10 to 19 year).

(b) Personal experience

In the last 44 years, 13 adolescents were referred for a second or third opinion for "unilateral GM" to the Division of Pediatrics and Adolescentology, Hospital of Ferrara and Outpatient Clinic of Private Accredited Quisisana Hospital of Ferrara. All patients were examined and followed by the same Pediatric Endocrinologist (VDS). The duration of "unilateral GM", at the time of first evaluation, was highly variable, ranging from 6 month to 4 years.

Ethics

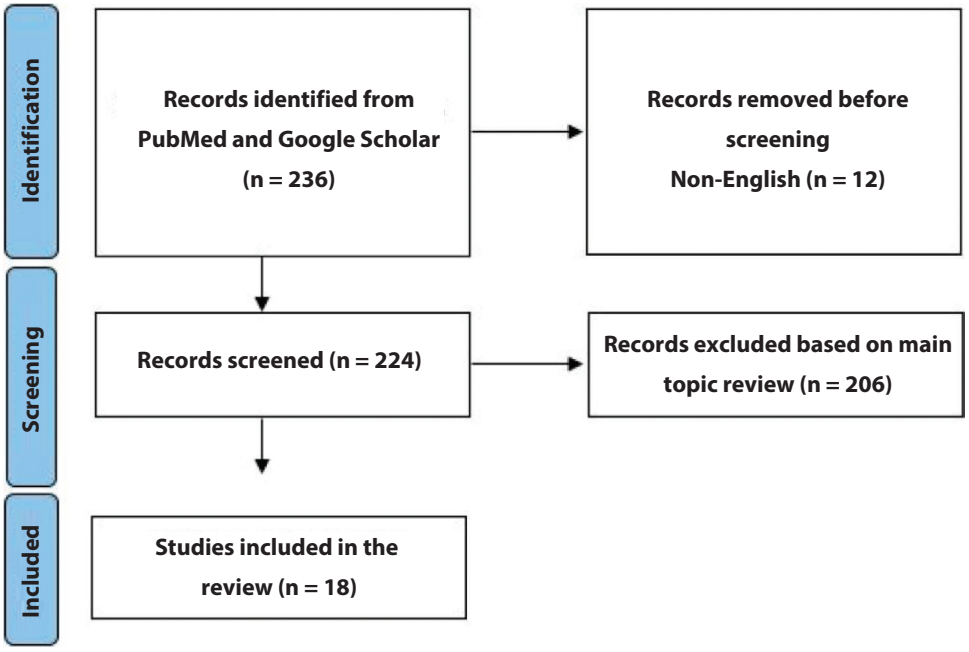
All procedures in our study were performed in accordance with the ethical standards of the Helsinki Declaration. Due to its retrospective design, not renewed contact with patients and non-experimental nature, a formal consent or a formal approval by a bioethics committee was not required. Patients or parents of patients gave consent for publication of medical histories and images.

Results

Of the 236 published studies found on GM during adolescence and examined meticulously by the authors, only 18 publications met the study research goal (Table 1).

Patients' ages, at first specialist evaluation of UBE, ranged from 10 to 19 years (mean age:14.0 ± 2.9 years). Almost all were case reports. As summarized chronologically in Tables 2A and 2B, the commonest reported diagnosis were: idiopathic or familial GM (no.1, 10,13-15,17) (33.3%), ductal carcinoma in situ (DCIS: no. 4,5, 8) (16.6%), breast sarcoma/carcinoma (no. 2,3,11) (16.6%). One patient with type-1 neurofibromatosis (no.12) developed breast pseudoangiomatous stromal hyperplasia. In two adolescents the UBE was due to medications (no.6,9) (11.1%) and in two was secondary to trauma (no.17,18) (11.1%). Regression of UBE was observed after medications withdrawal (18-35).

Table 1. Prisma flow diagram for the selection (included/excluded) of adolescent patients with unilateral breast enlargement (UBE).



Potential well-known risk factors for male breast cancer were reported in 1 patient (no.13).

UBE was noticed in 9/18 patients 2.9 ± 1.9 years before presentation to the physician. In particular, one patient (no.12) who developed carcinoma of breast, the interval from appearance of UBE and diagnosis of cancer was 5 years.

b. Personal experience

UBE was observed in 13 of 416 (3.1%) adolescents referred to our pediatric and adolescent endocrine clinic for GM . The age range at consultation was 13-19 years. Patients' demographic characteristics, family and personal history, pubertal status, entity of GM, hormone profiles, breast and testicular ultrasonography, and karyotype results (in 2 cases) were recorded. The sizes of the GM was evaluated with a caliper and classified into *mild* (slightly exceeding the mammary areola), *moderate* (exceeding areolar boundaries, with a diameter of 2-4 cm), *marked or macromastia* (enlargement and feminization associated with excess skin with a diameter > 5 cm). Pseudo-GM was distinguished from true GM based on the absence of a palpable lesion under the areola upon clinical examination or after evaluation with breast US.

Seven adolescents (46.6%) with marked GM or UBE due to pseudo -GM underwent excisional surgery. Histopathological diagnosis of idiopathic GM was done in 5 adolescents (38.4%) after surgical removal of the breast glandular tissue and subareolar fat. A marked UBE in 2 patients (15,3%) was due to cystic lymphangioma confirmed by histologic evidence.

Moderately marked UBE, secondary to treatment with androgens, was diagnosed in 2 β-thalassemic patients (15,3%) with hypogonadism (Figure 1). Moderate UBE was identified in 2 patients (15,3%) with Klinefelter syndrome associated with high estrogen/androgen ratio (14,36) (Figure 2) and in 1 patient (7.6%) with non-classical 21-hydroxylase deficiency (NC- 21-OH-D) which was thought to be the result of peripheral aromatization of androgens. The diagnosis of NC- 21-OH-D was substantiated by the finding of increased baseline of adrenocorticotropic hormone (ACTH)- stimulated 17-hydroxy-progesterone levels. In one adolescent the moderate UBE, a subareolar

Table 2 A. Review of literature (from 1957 to 2011) of adolescent males reported, at first evaluation, as gynecomastia (GM) or unilateral breast enlargement (UBE) by different authors (First part).

Number, Author, year of publication and age	**Patients' history and Physical examination**	**Risk factors and Investigations**	**Pathology/Diagnosis/ Follow-up**
1. James [18] (1957) 17-year-old	Remarkable degree of GM on the right side, started at the age of 15 years. The nipple was larger, and the areola was relatively bigger and darker.	Not reported. The brother had shown signs of GM at the age of 8 years. GM was progressive until surgical removal.	Speculative diagnosis: **Unilateral familial gynecomastia.**
2. Shackelford [19] (1952) 15-year-old	On two occasions during lacrosse practice "left breast" became ecchymotic.	Not reported. A hematoma was suspected. An attempt of aspiration revealed that the lesion was a tumor.	Histology diagnosis: Wildly growing **sarcoma.** Died seven weeks after operation. Metastases to the brain, liver, lungs and skin.
3. Kavalakat et al. [20] (2004) 17-year-old	Right GM (5 x 4 cm.) in the subareolar region with skin infiltration and multiple satellite nodules; multiple mobile ipsilateral axillary lymph nodes.	None. Previous FNA: negative.	Histology diagnosis: **Secretory carcinoma.** 10/12 axillary lymph nodes were involved.
4. Wadie et al. [21] 2005 16-year-old	Right GM (subareolar disc).	Not reported. Right subcutaneous mastectomy	Histology diagnosis. **DCIS.**
5. Chang et al. [22] (2008) 16 -year-old	Left unilateral GM	None.	Histology diagnosis: **Grade 1 DCIS.**
6, Karakurt et al. [23] (2009) 19-year-old	Unilateral GM during venlafaxine treatment	Not available. Increased serum prolactin, estradiol, and luteinizing hormone.	**Reduction of lump and normalization of hormone levels after drug withdrawal**
7. Durkin et al. [24] (2011) 14-year-old	Unilateral GM	Not reported. Surgical excision.	Histology diagnosis: **Intraductal papilloma.**
8. McCoubrey et al. [25] (2011) 17-year-old	Unilateral swelling of the left breast diagnosed as adolescent GM.	Not available. Four years later referred back to the breast surgery service	Histology diagnosis: **DCIS.**
9. Kumar et al. [26] (2011) 18-year-old	Unilateral and painless GM during re-treatment with isoniazid for pulmonary tuberculosis.	Not available	**Disappearance after a month of isoniazid cessation.**
10.Hoevenaren et al. 27 (2011) 11-year-old	12-month history of left breast enlargement and tenderness of the breast mass.	None. Endocrine, estrogen and progesterone receptors parameters were within normal limits. An abdominal CT scan excluded the presence of tumor.	Histology diagnosis: **Idiopathic gynecomastia** No evidence of malignancy. Partial resection of the gland: 5.0 × 3.0 × 2.5 cm.

Legend: DCIS, ductal carcinoma in situ; **US**: Ultrasonography of breast,

Table 2 B. Review of literature (from 2012 to 2022) of adolescent males reported, at first evaluation, as gynecomastia (GM) or unilateral breast enlargement (UBE) by different authors (UBE) (Second part).

Number, Author, year of publication and age	Patients' history and Physical examination	Risk factors and Investigations	Pathology/Diagnosis/ Follow-up
11. Hamza et al. [28] (2012) 11-year-old	5-years history of painless lump in the right breast, which increased gradually in size followed by bloody nipple discharge.	Not reported. On examination: 8 × 7 cm firm irregular breast mass, skin changes and fixation to the nipple-areola complex. Palpation of the right axilla revealed significant lymphadenopathy.	Histology diagnosis: **Breast carcinoma.** 12/15 identified axillary lymph nodes were involved.
12. Kimura et al. [29] (2012) 11-year-old	Reported mass in the right breast, which was first noticed at 7 years of age. US: indistinct homogenous low echoic lesion of ~ 10 mm in diameter. Biopsy was performed, and the mass recurred on the ipsilateral side after 4 years.	Type-1neurofibromatosis (NF-1). At 15 years, US revealed a highly echoic mass with circumscribed and irregular edges: 3.2.cm × 1.3 cm × 2.8 cm.	Histology diagnosis: **Pseudoangiomatous stromal hyperplasia**:
13. Ensat et al. [30] (2012) 12-year-old	Enlarged left breast noticed the first time at 6 years. He was suffering from ADHD and had been treated with methylphenidate since the age of 4 years.	None US: diffuse nodular breast gland hypertrophy (7 × 5 × 1 cm). Low echogenicity and dense stromal fibrosis with no evidence of calcification or cyst formation.	Histology diagnosis: **Idiopathic gynecomastia** No evidences of malignancy.
14. Ferraro et al. [31] (2014) 12-year-old	A reported 1 year history of left breast enlargement at the age of 12 years.	None. US: no abnormalities were reported. All endocrine parameters in the normal range.	Histology diagnosis: **Idiopathic gynecomastia**
15.Demirbilek et al.[32] (2014) 10.5-year-old	Left breast development was first noticed 1.5 years before presentation.	None Breast US showed a fibroglandular tissue 40 x10 mm in size, without any cystic or solid mass.	Histology diagnosis: **Idiopathic gynecomastia with intensive (3+) estrogen receptor expression** in 100% of periductal epithelial cells.
16. Pellegrin et al. [33] (2017) 11-year-old	Sudden painful enlargement of the left breast.	Not reported. US: subareolar hypoechoic and inhomogeneous area of 17 × 13 mm.	Diagnosis: **Subareolar hematoma.**
17.Park et al. [34] (2017) 16-year-old	5-year-history of an enlarged left breast. Palpation of the enlarged breast revealed firm glandular tissue. No bruising, discoloration, erythema, or signs of inflammation were observed.	None. US: ~1.3-cm area of breast glandular tissue in the left breast. Endocrine evaluation and human chorionic gonadotropin were within the normal range.	Histology diagnosis: **Idiopathic gynecomastia.** Firm glandular tissue (7.0 × 5.0 × 4.0 cm. weighing 221 g) The ducts were surrounded by dense fibrous stroma without nodules.
18. Laimon et al. [35] (2021) 10-year-old	Painful, slowly increasing left breast enlargement over the past 6 months. GM type 3 according to Ratnam's grading, with ecchymosis on the lower medial aspect of the left.	Not reported. US: prominent sub-areolar glandular tissue and diffuse homogeneous hypertrophy of the surrounding fibro-fatty tissue with normal echogenicity. No signs of malignancy. Testicular US was normal.	Histology diagnosis: **Breast ducts (adenosis)** with dense fibrosis and excess collagen due to repeated trauma along 1 year.

Legend: US: Ultrasonography of breast ; **CT**: computed tomography.

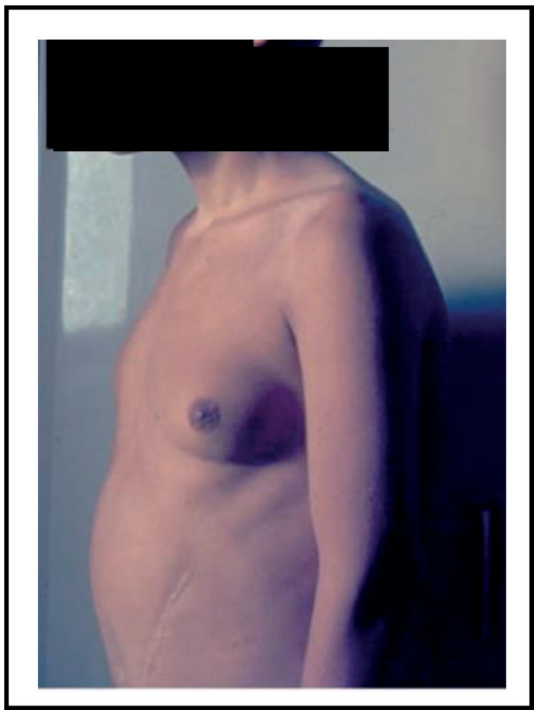


Figure 1. Marked unilateral breast enlargement (UBE) in a β- thalassemia major patient aged 17 years on treatment with depot testosterone for hypogonadotropic hypogonadism for two years (From: Soliman AT, De Sanctis V, Yassin M. Acta Biomed. 2017;88 (2): 204-13- De Sanctis V. Personal observation, with permission of Editor).

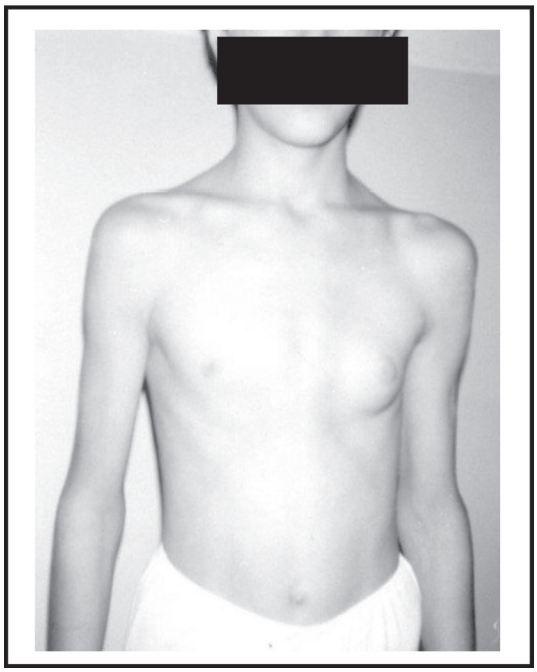


Figure 2. Moderate unilateral breast enlargement (UBE) in an adolescent aged 15 years with Klinefelter syndrome (De Sanctis V, personal observation).

hematoma due to injury was identified. A marked UBE in 2 patients (15,3%) was due to cystic lymphangioma confirmed by histologic evidence.

In general, a long delay was observed between the first appearance of UBE and request of consultation.

None of the seven adolescents who underwent surgery was obese and none had any atypical or malignant histologic finding. The two patients with Klinefelter syndrome, associated with high estrogen/androgen ratio, were treated with transdermal/gel testosterone therapy (36). After 4 months of treatment an evident improvement of GM was noticed, and no adverse effects or clinical breast manifestations were observed during the 6 years of follow-up. The 2 β-thalassemic patients with marked GM and high estradiol levels were treated with tamoxifen, after having excluded a tumour. After 3 months, both showed a partial regression of GM.

Case presentation of the two patients with cystic lymphangioma

The first boy, aged 13.5 years, was 162.6 cm tall (90 th-97th percentile), weighed 51,500 kg (90th percentile) with body mass index (BMI) of 19.5 kg/m^2. An initial "very mild breast enlargement" was observed by the parents for the first time at the age of 6-7 years. At first presentation, he was in advanced stage of pubertal maturation (testicular volume = 20 ml, Tanner' stage for pubic hair = 4). On clinical examination, he presented with a marked right pseudo-GM (7 cm in diameter) (Figure 3).

The second boy, aged 17.5 years, was 168.7 cm tall (10 th-25th percentile), weighed 62,300 kg (25th-50th percentile) with a body mass index (BMI) of 21.9 kg/m$^{2.}$ On examination, he was in advanced stage of puberty (testicular volume = 25 ml, Tanner' stage for pubic hair = 5). A moderate degree of right pseudo-GM (3-4 cm in diameter) was present. The parents reported that a "fluctuation" of the mammary gland was observed 6 years before the endocrine consultation.

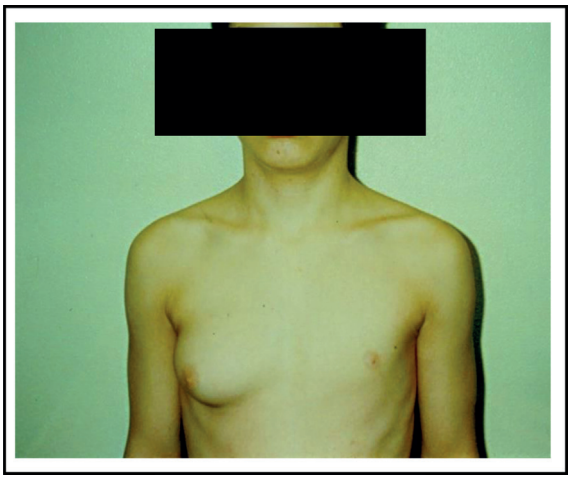


Figure 3. Unilateral breast enlargement (UBE), in a 13.5 year old patient, secondary to cystic lymphangioma (V. De Sanctis V, personal observation).

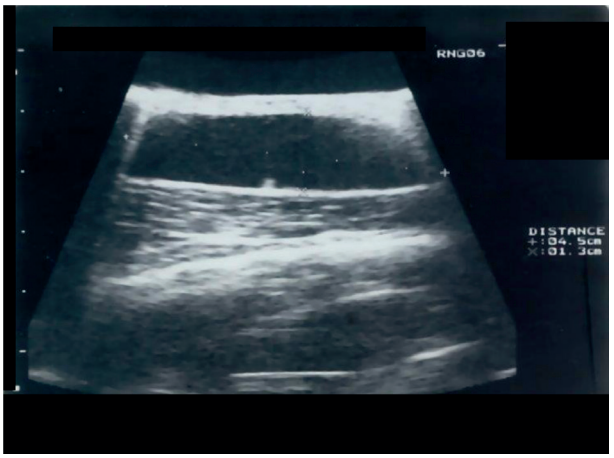


Figure 4. Ultrasound of the right breast region: presence of an oval anechoic formation measuring approximately 50 x 13 mm of the cystic type with hyperechoic sedimentation which departs from the posterior wall, with fairly defined contours.

In both cases, on clinical examination, the overlying skin presented a bluish marbling, the consistency of these formations was taut elastic, there was no pain, either spontaneous or on palpation.

Breast US showed, in correspondence with the palpable swelling, an oval anechoic area of cystic type with dimensions of 50 mm x 13 mm (Figure 4) and 45 mm x 20 mm, respectively.

In both patients the breast US was suggestive of UBE, presumably secondary to cystic lymphangioma (CL). The diagnosis of CL was confirmed by histological examination (Figures 5 and 6). The differential diagnoses of CL of the breast include simple cyst, abscess, hematoma, postoperative fluid collection, and hemangioma.

During the follow-up which lasted 10 and 12 years, respectively, no recurrences were observed in either subject.

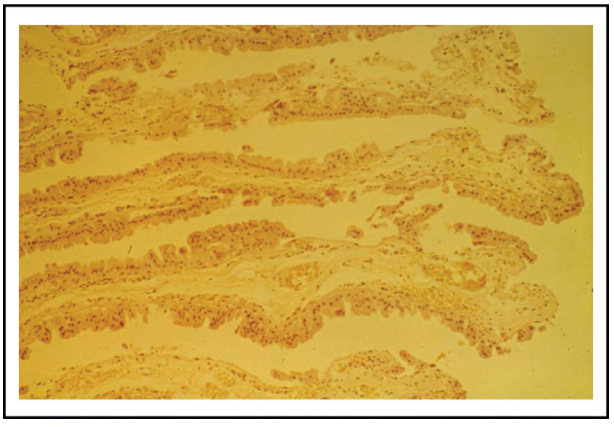


Figure 5. Histological examination of a 13.5 year old patient. Adipose tissue in the context of which there are ductal structures of the mammary type as well as a more voluminous cystic formation with thin, fibrous walls, covered by mono-stratified cubic epithelium, eosinophilic and circumscribed papillary elevations.

Discussion

Idiopathic UBE is a diagnosis of exclusion; a careful history, meticulous physical examination, and pertinent laboratory studies should be performed to exclude any possible pathologic cause. Commonly, this diagnosis is overlooked by many physicians. In our series, the general prevalence of UBE was 3.1% (13/416) adolescents referred for an endocrine consultation while the percentage of the idiopathic form was 38.4% (5/13).

The mechanisms involved in the development of idiopathic bilateral or UBE have not yet fully elucidated. The hormones involved in breast tissue physiology may be stimulatory (as estradiol and progesterone) or inhibitory (as testosterone), acting directly through

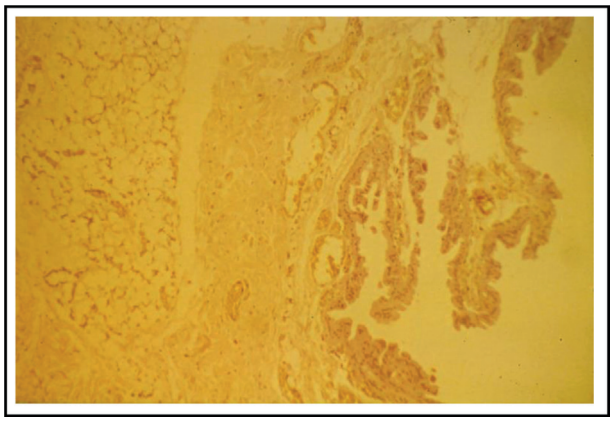


Figure 6. Histological examination of a 17.5 year old patient. Fibroadipose tissue in the context of which there is a cystic formation covered by epithelium consisting of cuboidal elements with an intensely eosinophilic cytoplasm with a round nucleus with decapitation aspects on the endoluminal margin and with the presence of an underlying layer of myo-epithelial cells. Papillary images are frequently seen. Rich vascular representation of the chorion underlying the epithelium.

their specific receptors on breast tissue cells (37). Receptors for insulin-like growth factor 1 (IGF-1), IGF-2, luteinizing hormone, and human chorionic gonadotropin have also been detected in breast tissue (38,39). Estrogens and progesterone apparently require the presence of growth hormone and IGF-1 to exert their stimulatory action on the breast (40).

Males produce estrogens primarily by converting peripheral androgens, testosterone, and androstenedione, to estradiol and estrone via the aromatase enzyme. Extra-glandular conversion of androgens (testosterone and androstenedione) to oestrogen occurs in the liver, skin, fat, muscle, bone, and kidney. All these tissues contain an aromatase enzyme, which is responsible for the steroids' conversion (14).

The pathophysiology of bilateral GM was considered to be due to disequilibrium between estrogen and androgen in the breast tissue or increased availability of oestrogen precursors from increased peripheral conversion to oestrogen (2,3,10). However, this explanation is not entirely applicable to unilateral GM. It has been suggested that this condition may be due to an overexpression of estrogen receptors in the mammary gland that increases the end-organ sensitivity and facilitates the development of GM in subjects who have low or normal circulating estrogen levels. Furthermore, the local tissue of the left and right breasts may have different distribution of fat, which contributes to varying levels of aromatase activity. The breast with a greater composition of fat might have higher growth that eventually manifests as unilateral GM (41).

The presence of hormone receptors in GM receptive cells supports the hypothesis that GM is steroid dependent. With regards to estradiol and androgen receptors, Calzada et al. (42) found that 85% of GM tissue contained estradiol or androgen receptors, and 40% contained both. The mean values of estradiol and androgen receptors in the cytosol were 65 ± 10 and 52 ± 5 fmol/mg protein, respectively. Nuclear androgen and estradiol receptor levels were 33 ± 7 and 67.5 ± 9 fmol/mg protein, respectively.

Pathological causes of UBE in adolescents are rare, may arise from a broad array of pathological conditions and are substantially different to those of prepubertal and advanced adult ages (15,16,43,44).

Therefore, if the cause of UBE is not obvious, further investigations are necessary. The history should include age of the patient, level of pubertal development, and presence of testicular mass(es). The past medical history, current medication and general health are of great importance to exclude evidence of a liver, kidney and thyroid disease. Alcohol misuse and illicit drugs, such as marijuana, heroin, and amphetamines should be considered as additional possible causes (45).

In our survey and personal experience, 10/31 UBE (32,2 %) were diagnosed as cases of idiopathic or familial GM in one adolescent (1/31). In 3/31 UBE (9.6 %) was due to breast sarcoma/carcinoma. One patient (11-years old) had a 5-years history of painless lump in the right breast, which increased gradually in size followed by bloody nipple discharge.

Breast tumors comprise only 0.2% of all male cancers. In a 20-year national registry study of surgically excised breast specimens with the diagnosis of bilateral GM, the overall prevalence of invasive carcinomas was 0.11% and of *in situ* carcinomas (DCIS) was 0.18% (45). Although the cases described in the literature are mainly a few case series or case reports (46), and the prognosis in adults with pure DICS (defined as

a lesion confined to the breast ducts, without invasive features or metastatic potential) is excellent, with 5-year overall survival of 93.3%. One adult patient had an ipsilateral recurrence with infiltrating carcinoma in the same breast after 14 years (47).

Examination of breast should include breast size, shape, symmetry, skin appearance, and palpation of the regional lymph nodes. The probable signs of malignancy are: 1) hard or irregular breast tissue, 2) eccentric breast mass, 3) rapid enlargement, 4) fixed mass, 5) nipple secretion or skin abnormalities, 6) pain, 7) mass >5 cm, 7) axillary lymphadenopathy, and 8) persistent UBE (47, 48). Additional risk factors for breast cancer in men are: Klinefelter syndrome, androgen receptor mutation, history of chest irradiation, family history of breast cancer (particularly mutations of the BRCA2 gene) and Cowden syndrome (49).

There are no well-established algorithms for evaluating UBE in adolescents and several parts of the evaluation process remain controversial. Some authors recommend an endocrine investigation (16,41), a breast US to evaluate the indication for a cyto-microhistological sampling (47), a testicular US and laboratory measurements of serum tumoral markers (50). The imaging characteristics of male breast lesions are similar to those of the female breast. If all the evaluated data are normal, UBE is considered idiopathic, which is the most common type. Underlying causes should be corrected, when possible while surgery can be offered to patients with persistent or atypical signs and/or symptoms.

In conclusion, and as shown in this study, the long duration of UBE, before diagnosis fully supports the need for better attention and further investigation of this condition. A prompt diagnosis is crucial to avoid any evolution towards an aggressive form of the disease (46,47). Referral to a medical endocrinologist is advised in the presence of abnormal endocrine (hormonal) results. The presence of a testicular mass on clinical or US examination, and/or the presence of increased AFP or β-HCG levels should prompt urgent referral to a specialist. Finally, we believe that for optimal management of this condition better collaboration between primary care physician and specialists is mandatory.

Funding: none

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contributions: Conceptualization: All Authors; Review of data and analysis of literature: VDS; Writing original draft preparation: VDS; Revision of manuscript for important intellectual content and editing: AS, SD, PT, SDM and CK; All authors have read and approved the final version of the manuscript, ensuring that questions related to the accuracy and integrity of any part of the work were appropriately analyzed and discussed.

References

1. Kanakis GA, NordkapL, Bang Ak, et al. EAA clinical practice guideliness- gynecomastia evaluation and management. Andrology 2019;7: 778-93 doi 10.1111/andr.12636.
2. Günhan-Bilgen I, Bozkaya H, Ustün EE, Memiş A. Male breast disease: clinical, mammographic and ultrasonographic features. Eur J Radiol. 2002;43:246–55. doi:10.10167a0720-048x(01)00483-1.
3. Kim MS, Kim JH, Lee KH, Suh YJ. Incidental Gynecomastia on Thoracic Computed Tomography in Clinical Practice: Characteristics, Radiologic Features, and Correlation With Possible Causes in South Korean Men. Am J Mens Health. 2020;14(3):1557988320908102. doi: 10.1177/ 155798 8320 908102.
4. Kumanov P, Deepinder F, Robeva R, Tomova A, Li J, Agarwal A. Relationship of adolescent gynecomastia with varicocele and somatometric parameters: a cross-sectional study in 6200 healthy boys. J Adolesc Health 2007;41(2):126–31. doi:10.10167j.jadohealth.2007.03.010.
5. Klang E, Kanana N, Grossman A, et al. Quantitative CT assessment of gynecomastia in the general population and in dialysis, cirrhotic, and obese patients. Acad Radiol. 2018; 25(5):626–35. doi:10.1016/j. acra.2017.11.008.
6. Lorek M, Tobolska-Lorek D, Kalina-Faska B, Januszek-Trzciakowska A, Gawlik A. Clinical and Biochemical Phenotype of Adolescent Males with Gynecomastia. J Clin Res Pediatr Endocrinol. 2019; 11(4):388-94.doi:10.4274/jcrpe.galenos.2019.2019.0027.
7. Akgül S, Derman O, Kanbur N. Pubertal gynecomastia: Years of progress-the Hacettepe experience. Int J Adolesc Med Health. 2017;31 /j/ijamh. 2019.31.issue-3/ijamh-2017-0011/ijamh-2017-0011.xml. doi: 10.1515/ijamh-2017-0011.
8. Acharya SV. Clinical features, presentation and hormonal parameters in patients with pubertal gynecomastia. J Family Med Prim Care. 2021;10(2):648-51.doi: 10.4103/jfmpc.jfmpc_1987_20.

9. Soliman AT, De Sanctis V, Yassin M. Management of Adolescent Gynecomastia: An Update. Acta Biomed. 2017;88(2):204-13. doi: 10.23750/abm.v88i2.6665.
10. Bannayan GA, Hajdu SI. Gynecomastia: clinicopathologic study of 351 cases. Am J Clin Pathol 1972;57(4):431–7. doi.10.1093/ajcp/57.4.431.
11. Nicolis GL, Modlinger RS, Gabrilove JL. A study of the histopathology of human gynecomastia. J Clin Endocrinol Metab. 1971;32:173–8.doi:10.1210/jcem-32-2-173.
12. Önder Ö, Azizova A, Durhan G, Elibol FD, Akpınar MG, Demirkazık F. Imaging findings and classification of the common and uncommon male breast diseases. Insights Imaging. 2020;11(1):27.doi: 10.1186/s13244-019-0834.
13. Draghi F, Tarantino CC, Madonia L, Ferrozzi G. Ultrasonography of the male breast. J Ultrasound. 2011;14(3):122-9.doi: 10.1016/j.jus.2011.06.004.
14. Swerdloff RS, Ng CM. Gynecomastia: etiology, diagnosis, and treatment. In Endotext [Internet]. Eds Feingold KR, Anawalt B, Boyce A, et al. South Dartmouth (MA): MDText.com, Inc. 2019.
15. Lapid O, Jolink F, Meijer SL. Pathological findings in gynecomastia: analysis of 5113 breasts. Ann Plast Surg. 2015;74(2):163–6.doi.10.1097/SAP.0b013e3182920aed.
16. Lemaine V, Cayci C, Simmons PS, Petty P. Gynecomastia in adolescent males. Semin Plast Surg. 2013; 27(1):56-61. doi: 10.1055/s-0033-1347166.
17. World Health Organization. Young people's health – a challenge for society. Report of a Study Group on Young People and Health for All by the Year 2000, Technical Report Series, No. 731. Geneva: World Health Organization, 1986 <http://whqlibdoc.who.int/trs/ WHO_TRS_731 .pdf> (Version current at September 8, 2003).
18. James T. Familial unilateral gynaecomastia in an adolescent. S Afr Med J.1957;782-2.doi: AJA2078 513 5_45496.
19. Shackelford RT (discussion). In: Hartman AM, Magrish P. Carcinoma of breast in children: case report: six-year-old boy with adenocarcinoma. Ann Surg. 1955;141(6):792-7. Ann Surg.1955;141(6): 792-8. doi:10. 1097/00000658 -195506000-00005.
20. Kavalakat AJ, Covilakam RK, Culas TB. Secretory carcinoma of breast in a 17-year-old male. World J Surg Oncol. 2004;2:17.doi:10.1186/1477-7819-2-17.
21. Wadie GM, Banever GT, Moriarty KP, Courtney RA, Boyd T. Ductal carcinoma in situ in a 16-year-old adolescent boy with gynecomastia: A case report. J Pediatr Surg. 2005;40:349-53. doi:10.1016/j.jpedsurg. 2005.05.026.
22. Chang HL, Kish JB, Smith BL, Goldstein AM. A 16-year-old male with gynecomastia and ductal carcinoma in situ. Pediatr Surg Int. 2008;24:1251–3. doi.org/10.1007 /s00383-008-2246-1.
23. Karakurt F, Kargili A,Uz B, et al. Venlafaxine-induced gynecomastia in a young patient: a case report. Clin Neuropharmacol.2009,32(1):51-2.doi:10.1097/WNF .0B12E181679126.
24. Durkin ET, Warner TF, Nichol PF.Enlarging unilateral breast mass in an adolescent male: an unusual presentation of intraductal papilloma.J Pediatr Surg. 2011; 46 (5):e33-e5. doi.org/10.1016/j. jpedsurg. 2011.02.068.
25. McCoubrey G, Fiddes R, Clarke PJ, Coleman DJ. Ductal carcinoma in situ of the male breast presenting as adolescent unilateral gynaecomastia. J Plastic Reconstr Aesthet Surg. 2011;64:1684-6.doi.org/10.1016/j. bjps.2011.04.024.
26. Kumar L, Gupta R, Puri MM, et al. Unilateral and painless development of isoniazid induced gynecomastia during re-treatment of pulmonary tubercolosis. J Assoc Physician India. 2011;59: 733-5.PIMD:22616343.
27. Hoevenaren IA, Schott DA, Otten BJ, Kroese-Deutman HC. Prepubertal unilateral gynecomastia: a report of two cases. Eur J Plast Surg. 2011;34(5):395-8. doi: 10.1007 /s00238-010-0469-6.
28. Hamza AA, Ngwangki LS, Taha O. Breast carcinoma in a boy with metastatic axillary lymph nodes. Sudan J Paediatr. 2012;12(1):89-92. PMID: 27493334.
29. Kimura S , Tanimoto A , Shimajiri S, et al. Unilateral gynecomastia and pseudoangiomatous stromal hyperplasia in neurofibromatosis: Case report and review of the literature. Pathol Res Pract.2012;208(5): 318-22.doi:10.1016/j .prp.2012.03.003.
30. Ensat F, Edelbauer M, Wechselberger G. Unilateral gynecomastia in a prepubertal boy. Eur J Pediatr. 2012;171:197. doi.org/10.1007/s00431-011-1546-y.
31. Ferraro GS, De Francesco F, Romano T, et al. Clinical and surgical management of unilateral prepubertal gynecomastia. Int J Surg Case Rep. 2014;5(12):1158-61. doi .org/10.1016/j.ijscr.2014.11.040.
32. Pellegrin MC, Naviglio S, Cattaruzzi E, Barbi E, Ventura A. A Teenager with Sudden Unilateral Breast Enlargement. J Pediatr. 2017;192:394. doi.org/10.1016/j.jpeds.2016.11.044.
33. Demirbilek H, Bacak G, Baran RT, et al. Prepubertal unilateral gynecomastia: report of 2 cases. J Clin Res Pediatr Endocrinol. 2014;6(4):250-3.doi: 10.4274/Jcrpe.1477.
34. Park SH, Kim JH, Choi HJ, Lee YM, Choi YA. Idiopathic Unilateral Gynecomastia in an Adolescent Male: A Case Report. Arch Aesthetic Plast Surg. 2017;23(2):101-3. doi. org/10.14730/aaps.2017.23.2.101.
35. Laimon W, El-Hawary A, Aboelenin H, et al. Prepubertal gynecomastia is not always idiopathic: case series and review of the literature. Eur J Pediatr.2021;180 (3) 977- 82. doi. org/10.1007/s00431-020-03799-x.
36. Chang S, Skakkebaek A, Davis SM, Gravholt CH. Morbidity in Klinefelter syndrome and the effect of testosterone treatment. Semin Med Genet. 2020;184(2):344-55. doi: 10.1002/ajmg.c.31798.
37. Nuttall F Q. Gynecomastia. Mayo Clin Proc. 2010;85(10): 961–2. doi: 10.4065/mcp.2010.0093.
38. Carlson HE, Kane P, Lei ZM, Li X, Rao CV. Presence of luteinizing hormone/human chorionic gonadotropin receptors in male breast tissues. J Clin Endocrinol Metab. 2004;89(8):4119–23. doi:10. 1210/jc.2003-031882.
39. Narula HS, Carlson H E. Gynaecomastia - Pathophysiology, diagnosis and treatment. Nature Rev Endocrinol.2014; 10(11):684–98. doi: 10.1038/nrendo.2014.139.

40. Kleinberg DL, Feldman M, Ruan W. IGF-I: An essential factor in terminal end bud formation and ductal morphogenesis. Journal of Mammary Gland Biology and Neoplasia. 2000;5 (1):7-17. doi: 10.1023/ A:1009 507030633.
41. Sakulterdkiat T, Romphothong K, Chatchomchuan W, et al. Unilateral gynecomastia as an initial presentation of hyperthyroid Graves' disease. Endocrinol Diabetes Metab Case Rep. 2021;2021:20-0140. doi: 10.1530/EDM-20-0140.
42. Calzada L,Torres-Calleja J, Martinez JM, Pedron N. Measurement of androgen and estrogen receptors in breast tissue from subjects with anabolic steroid-dependent gynecomastia. Life Sci. 2001;69:1465-9.doi: 10. 10167s0024-3205 (01)01227-9.
43. Costanzo PR, Pacenza NA, Aszpis SM,et al. Clinical and Etiological Aspects of Gynecomastia in Adult Males: A Multicenter Study. Biomed Res Int. 2018;2018:8364824. doi: 10.1155/2018/8364824.
44. Elazizi L, Essafi MA, Hanane A, Aynaou H, Salhi H, El Ouahabi H. A Clinical, Etiological, and Therapeutic Profile of Gynecomastia. Cureus. 2022;14(8):e27687. doi:10.7759 /cureus.27687.
45. Bromley HL, Dave R, Lord N, Wright P, Rowland M, Gandhi A. Gynaecomastia: when and why to refer to specialist care. Br J Gen Pract. 2021;71(705):185-8. doi: 10.3399/bjgp21X715577.
46. Hittmair AP, Lininger RA, Tavassoli FA . Ductal carcinoma in situ (DCIS) in the male breast: a morphologic study of 84 cases of pure DCIS and 30 cases of DCIS associated with invasive carcinoma—a preliminary report. Cancer. 1998;83(10):2139-49.doi:10.1007/s10549-022-06689-y.
47. Nicosia L, Lissidini G, Sargenti M, et al. Ductal carcinoma in situ of the male breast: clinical radiological features and management in a cancer referral center. Breast Cancer Res Treat.2022; 196: 371-7.doi.org/10. 1007/s10549-022-06689-y.
48. Mathew J, Perkins GH, Stephens T, Middleton LP, Yang WT. Primary breast cancer in men: clinical, imaging, and pathologic findings in 57 patients. Am J Roentgenol. 2008;191(6):1631-9.doi:10.2214/ ajr. 08.1076.
49. White J, Kearins O, Dodwell D, Horgan K, Hanby AM. Male breast carcinoma: increased awareness needed. Breast Cancer Res.2011;13:219.doi.org/10.1186/bcr2930.
50. Daniels IR, Layer GT. Testicular tumours presenting as gynaecomastia. Eur J Surg Oncol. 2003;29:437- 9. doi: 10.1016/S0748-7983(03)00004-0.

Correspondence:
Received: 22 January 2023
Accepted: 22 February 2023
Vincenzo De Sanctis, MD
Coordinator of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) and Adolescent Outpatient Clinic, Quisisana Hospital
Ferrara, Italy
Via Paolo V, 25 - 44121 Ferrara, Italy
Tel: +39 0532 770243
E-mail: vdesanctis@libero.it