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Bilateral Gynecomastia in an Adolescent with Neurofibromatosis Type 1: An Unusual Presentation

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Abstract **Case Report**

Gynecomastia is a benign proliferation of breast glandular tissue in males, common during adolescence but warranting investigation when persistent or associated with a specific pathological condition. Neurofibromatosis type 1 (NF1) is a multisystemic genetic disorder, whose endocrine manifestations remain rare and poorly described. We report the case of a 17-year-old patient, followed since the age of one year for NF1, presenting with progressive bilateral gynecomastia with normal endocrine, hepatic, and tumor findings. This case illustrates the diagnostic difficulties posed by idiopathic gynecomastia in a specific genetic context and highlights the importance of careful, multidisciplinary management.

Keywords: Gynecomastia, adolescent, neurofibromatosis type 1, normal endocrine assessment, puberty, surgery.

INTRODUCTION

Gynecomastia is a benign enlargement of male breast tissue caused by an imbalance between estrogenic and androgenic activity. It may be physiological, occurring transiently during infancy, adolescence, or aging, or pathological, secondary to medications, endocrine disorders, systemic diseases, or genetic conditions [1,2]. However, persistent, bilateral gynecomastia or gynecomastia associated with a chronic disease requires rigorous etiological evaluation to exclude a secondary cause.

NF1 is an autosomal dominant genetic disorder related to a mutation in the NF1 gene, characterized by skin, neurological, and bone manifestations. Although mainly known for its neurocutaneous involvement, NF1 can also be accompanied by endocrine disorders, particularly growth or puberty abnormalities, often linked to hypothalamic-pituitary axis involvement [3,4]. However, the association between NF1 and gynecomastia remains exceptional and poorly documented in the literature.

We report the case of an adolescent who has been monitored for NF1 since the age of one, presenting with persistent bilateral gynecomastia despite normal endocrine, hepatic, and tumor findings, illustrating the diagnostic difficulties of idiopathic gynecomastia and suggesting a possible pathophysiological link with NF1.

CLINICAL CASE

We report the case of a 17-year-old adolescent who had been followed since the age of one for NF1, diagnosed on the basis of clinical criteria combining multiple café-au-lait spots (more than 6), axillary and inguinal freckling, and several cutaneous neurofibromas (**Figure 1**). The patient had no personal or family history of endocrine disorders, and was not taking any medications likely to induce gynecomastia.

He consulted for a bilateral and slowly progressive increase in breast volume, which had been developing since a year ago. This gynecomastia was initially painless, with no local inflammatory signs or nipple discharge, but it had a major psychological impact. Over the last six months, the clinical evolution has been marked by an increase in bilateral breast volume, which has become painful.

The clinical examination revealed bilateral, symmetrical gynecomastia of glandular consistency, with no suspicious masses or axillary lymphadenopathy (**Figure 2**). Pubertal development was complete and harmonious (Tanner stage G5P5), with normal-sized, well-positioned testicles. The assessment included a hormonal evaluation revealing normal gonadotropic function, including age-appropriate total testosterone levels, as well as normal LH, FSH, and estradiol levels.

Prolactin levels, thyroid function, and liver and kidney function tests were also normal.

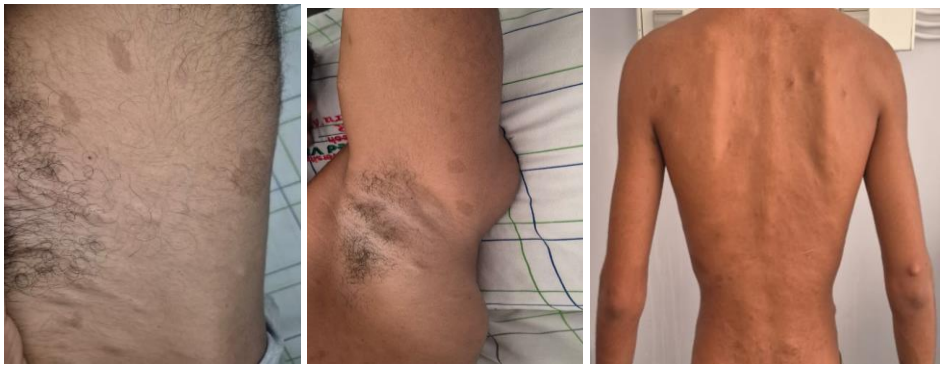

Figure 1: Clinical diagnostic criteria for NF1 observed in our patient: multiple café-au-lait spots (A, B, C), axillary and inguinal freckling (A)(B), and several cutaneous neurofibromas (C)

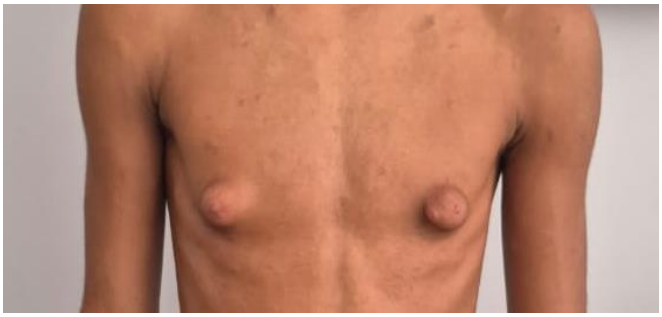

Figure 2: Clinical examination revealing symmetrical bilateral gynecomastia in a patient with NF1

The assessment included a hormonal evaluation revealing normal gonadotropic function, including age-appropriate total testosterone levels, as well as normal LH, FSH, and estradiol levels. Prolactin levels, thyroid function, and liver and kidney function tests were also normal.

Breast ultrasound revealed bilateral hypertrophy of the glandular tissue, with no nodular images or signs of malignancy, confirming the diagnosis of true gynecomastia. Testicular ultrasound did not reveal any focal lesions or signs suggestive of a testicular tumor.

In the absence of biological or radiological abnormalities, a diagnosis of persistent idiopathic gynecomastia occurring in the context of NF1 was made. Aesthetic surgery was proposed due to the significant psychosocial impact, with anatomical findings consistent with bilateral gynecomastia without signs of malignancy.

DISCUSSION

Gynecomastia is a benign proliferation of mammary glandular tissue in males, resulting from a relative imbalance between the action of estrogen and androgen in the mammary tissue. It is a common condition in adolescence, most often occurring transiently during pubertal maturation, with a prevalence of up to 50-60% depending on the series [1][2]. In most cases, this pubertal gynecomastia regresses spontaneously within two years, without the need for further investigation.

However, if gynecomastia persists beyond 12 to 18 months, is bilateral, or occurs in a specific clinical context, a thorough etiological investigation is required. The main purpose of this investigation is to exclude secondary causes, particularly endocrine, tumor, or drug-related causes, as early recognition of these causes is crucial for management and prognosis [5]. In the reported case, the absence of biological abnormalities in gonadotropic, thyroid, prolactin hormone levels, and tumor assessment, combined with a normal testicular examination, allows us to rule out the main secondary etiologies typically described in adolescents. This situation points to a diagnosis of persistent idiopathic gynecomastia, a condition that remains common in adolescence, even in the presence of an associated pathological condition.

NF1 is an autosomal dominant genetic disorder resulting from a mutation in the NF1 gene, which requires at least two of the following criteria for diagnosis [6]: the presence of at least six café-au-lait spots, at least two neurofibromas or at least one plexiform neurofibroma, freckles in the axillae or inguinal region, an optic glioma, at least two Lisch nodules, sphenoid wing dysplasia or thinning of the cortex of long bones with or without pseudarthrosis, and a first-degree relative who also meets the above criteria

for NF1. Our patient had the diagnostic criteria for NF1, with the typical café-au-lait spots, neurofibromas, and bilateral gynecomastia. Genetic testing was not performed due to the limitations of its availability in our setting.

NF1 associated with prepubertal gynecomastia has been described in several case reports. Murat *et al.,*[7] reported the observation of a 10-year-old boy who presented with a 3 cm solid breast mass, which pathological examination confirmed to be a NF1. And a case of severe unilateral gynecomastia in a 14-year-old adolescent with NF1 undergoing mastectomy, reported by Fangjian Shang et al [8]. Similar observations were published by Damiani and Eusebi [9], describing bilateral gynecomastia associated with breast neurofibromatosis in a 6-year-old boy. In addition, a series of six male patients presenting with both gynecomastia and neurofibromatosis was reported, with strictly normal hormone levels in all patients [10,11].

In patients with NF1, the pathophysiology of gynecomastia remains poorly understood and is based primarily on hypotheses. NF1 is a complex neurocutaneous disorder that can be accompanied by central nervous system involvement that may interfere with hypothalamic-pituitary regulation. Subclinical disorders of the gonadotropic axis have been reported, particularly in patients with optic chiasm or hypothalamic lesions, which can result in abnormalities of puberty or growth [3]. Even in the absence of hormonal abnormalities detectable by standard assays, subtle central dysregulation cannot be completely ruled out.

In addition, peripheral mechanisms independent of circulating hormone concentrations must be considered. Local hypersensitivity of breast tissue to estrogen, linked to increased expression or activity of estrogen receptors, has been suggested as a potential mechanism in certain forms of idiopathic gynecomastia. Similarly, a local increase in the aromatization of androgens into estrogens in adipose or breast tissue could explain glandular development in the absence of systemic hyperestrogenism [5]. These tissue mechanisms, which are difficult to objectively assess in clinical practice, may play a particular role in patients with complex genetic diseases such as NF1.

Beyond pathophysiological considerations, the psychological impact of gynecomastia in adolescents should not be underestimated. Several studies have shown that gynecomastia can be associated with impaired self-esteem, social anxiety, and isolation, effects that may be exacerbated in patients with chronic or visible genetic diseases such as NF1 [2]. This psychosocial dimension warrants a comprehensive and individualized approach, incorporating not only clinical and endocrine monitoring, but also appropriate psychological support.

In adolescents with stable bilateral idiopathic gynecomastia without biological or radiological abnormalities, active surveillance is the first-line strategy, as approximately 75% to 90% of cases regress spontaneously within 1–3 years. Management consists of regular clinical monitoring, focusing on changes in breast size and psychosocial integration, as well as targeted psychological support given the emotional impact and anxiety associated with this condition [12].

Surgery (breast reduction by glandular excision ± liposuction) is reserved for persistent cases after completion of pubertal maturation or when the psychosocial impact is significant and the gynecomastia is stable. Surgical techniques must be adapted to the patient's morphology, with particular attention paid to the aesthetic appearance and physical development of the adolescent [13].

Pharmacological options (e.g., antiestrogens such as tamoxifen or raloxifene) have been studied in adolescents with sometimes favorable results in reducing breast size, but their use is not universally approved due to a lack of robust data on long-term efficacy and safety. Nevertheless, early treatment may be considered in selected cases with bothersome gynecomastia and no spontaneous response [12].

Long-term follow-up should include ongoing psychosocial assessment and monitoring of androgenic, and endocrine signs, particularly in the context of an underlying genetic disorder such as NF1. It is also recommended to periodically reassess the indication for therapeutic intervention if gynecomastia persists beyond two to three years without spontaneous regression [10].

CONCLUSION

Idiopathic bilateral gynecomastia in adolescents, including in the context of NF1, is most often benign and spontaneously regressive. After rigorous exclusion of secondary causes. Management is based mainly on clinical monitoring and psychosocial support, given the frequent impact at this age [1,10]. Surgical management for cosmetic purposes may be considered in cases of persistence after the end of pubertal maturation and significant psychosocial impact, in accordance with current recommendations [14].

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