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CLINICAL MANAGEMENT OF ENDOCRINE DISEASES

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Idiopathic gigantomastia: newer mechanistic insights implicating the paracrine milieu

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Abstract

Purpose Gigantomastia refers to pathological breast enlargement usually occurring in the peripubertal or peripartum period. Idiopathic gigantomastia, however, is a rare entity with hypotheses citing local expression of hormones and growth factors in causing this disease, none of which have been systemically analysed. The purpose of this study was to delve deeper into the mechanistic pathways causing this condition.

Methods Herein, we describe three patients of idiopathic gigantomastia, all of whom had had normal puberty and uneventful pregnancies. Further, one of the patients had postmenopausal gigantomastia which is extremely rare, with only four cases described in the literature. Serum markers of autoimmunity, incriminated hormones and growth factors analysed, were normal in all the cases. Breast tissue specimens were subjected to histopathological examination and immunohistochemistry for ER, PR and Her-2-Neu. Quantitative immunofluorescence for aromatase, IGF2, EGFR, TGF-β, PDGFR-α, β, IGF1 and PTHrP was also performed.

Results Of these, the tissue expression of aromatase, IGF2, EGFR, TGF-β, PDGFR-α and β were found to be upregulated, whereas IGF1 and PTHrP were comparable to normal breast.

Conclusion This observation that paracrine overexpression of these factors is responsible for the pathogenesis of apparently idiopathic gigantomastia may have therapeutic ramifications in the future for patients with this debilitating condition.

Abbreviations

PTHrP	Parathyroid hormone related peptide
BMI	Body mass index
E2	Estradiol
LH	Luteinising hormone
FSH	Follicle stimulating hormone
IGF1	Insulin like growth factor-1
IGF2	Insulin like growth factor-2
GH	Growth hormone
fT3	Free Tri-iodo thyronine
fT4	Free Tetra-iodo thyronine
TSH	Thyroid stimulating hormone
HbA1c	Glycated hemoglobin
HOMA-IR	Homeostasis model assessment for insulin resistance
BIRADS	Breast imaging reporting and data system
TPO	Thyroid peroxidase
ANA	Anti-nuclear antibodies
SMA	Anti-smooth muscle antigen
LKM	Anti-liver kidney muscle antibody
AMA	Anti-mitochondrial antibody
CEA	Carcinoembryonic antigen
α-FP	Alpha fetoprotein
NAC	Nipple areola complex
IHC	Immunohistochemistry
ER	Estrogen receptor
PR	Progesterone receptor

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Her-2-Neu	Herceptin
IF	Immunofluorescence
PDGFR-α	Platelet derived growth factor-alpha
PDGFR-β	Platelet derived growth factor-beta
VEGF	Vascular endothelial growth factor
TGF-β	Transforming growth factor-beta
IG	Idiopathic gigantomastia

Normal values

17-β E2	7.6–42.6 pg/ml
Progesterone	<1 ng/ml
LH	2.4–12.6 mIU/ml
FSH	3.5–12.5 mIU/ml
GH	<1 ng/ml
Prolactin	5–25 ng/ml
fT3	2.3–4.2 pg/ml
T4	0.89–1.76 ng/dl
TSH	0.4-4.2 mIU/l
TPO	<34 IU/ml
HbA1c	<5.7%
CA125	0–35
CA19-9	0–27
CEA	3.8–5.5
α-FP	0–5.8
IGF1	64–262 ng/ml
HOMA-IR	<2—normal, 2 to 3—mild insulin resistance, 3 to 5—moderate insulin resistance, >5—severe insulin resistance

Introduction

Gigantomastia refers to excessive breast enlargement due to hypertrophy rather than hyperplasia and is usually an extreme form of macromastia. The definition is variable, but surgical removal of at least 1500 gm of mammary tissue is accepted as reasonable evidence of this condition. Commonly, it is noted during puberty and pregnancy. But, there are many other causes mentioned in the literature [1–4]. Idiopathic gigantomastia, however, is a rare entity with only a handful of cases reported in the literature.

Herein, we report three cases of the rare entity of idiopathic gigantomastia including one in a postmenopausal woman, which is still rarer. Further, immunofluorescence and quantification of these factors performed on tissue samples of these patients is a novel method to assess the local milieu in the breast.

Material and methods

Three patients described herein all satisfied the criteria of idiopathic gigantomastia and reduction mammoplasty was done in the first case only as the other two did not provide consent. All three cases are described below.

Case 1

A 35-year-old unmarried, nulliparous female presented with painless and progressive breast enlargement with recurrent superficial ulcerations for the past 4 years. There was no history of galactorrhoea. She had attained menarche at the age of 13 years with regular menstrual cycles. She did not have history of any chronic drug intake including oral contraceptives or estrogen. There was no history suggestive of autoimmune disease and family history was non-contributory. Her condition had gradually progressed to cause upper back pain for the past 6 months with marked impairment of her psychological, social and professional life. She had been prescribed danazol, but did not experience significant benefit. On examination, she was overweight (BMI of 28.4 kg/m^2). Breast examination revealed large, asymmetric, pendulous breasts bilaterally (Fig. 1a) with firm, mobile non-tender nodules. There was no axillary lymphadenopathy, stigmata of

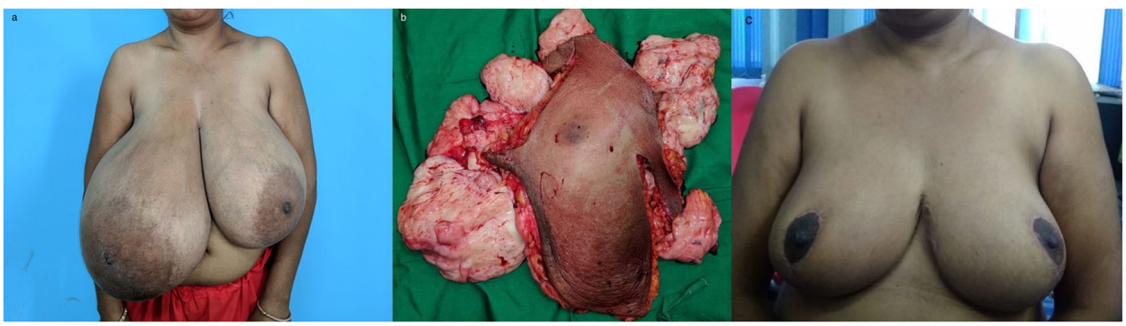

Fig. 1 **a** Bilateral, asymmetric idiopathic gigantomastia in patient 1. Note is made of dilated and tortuous superficial veins, enlarged nipple-areola complex with sternal to nipple distances of 42 and 35 cm and nipple-inframammary fold distances of 35 and 24 cm (of the right and left breasts, respectively). The nipple-areola complex on both sides was stretched with dilated veins. **b** Intra-operative specimen following bilateral reduction mammoplasty, with excision of 7.5 kg breast tissue, ~11% of body weight. 3 kg breast tissue was removed from left side and 4.5 Kg breast tissue from right side. **c** 3 months post-op status of the patient showing normal breasts with preserved contours, areolae and minimal scar

autoimmune disease or spinal abnormalities. Her hormonal profile was normal: LH and FSH 13 mIU/l and 15 mIU/l, 17-β E2 5 pg/ml, testosterone 0.8 nmol/l, DHEAS 206 µg/dl, progesterone 0.3 ng/ml and prolactin level of 39 ng/ml. fT3 was 2.78 pg/ml, fT4 was 0.96 ng/dl and TSH was 2.1 mIU/l. IGF1 was 115 ng/ml and GH was 0.05 ng/ml. HbA1c was 4.7% and HOMA-IR was 4.56 (3-5 suggests moderate insulin resistance). Autoantibodies (TPO, ANA, SMA, LKM and AMA) were negative. Serum tumour markers (CA-125, CA-19-9, CEA and α-FP) were non-contributory. Ultrasound of both breasts revealed multiple fibroadenomas, while mammography showed dense fibroglandular pattern with multiple hypoechoic lesions, BIRADS 3. Benign fibroepithelial lesions were noted on core biopsy. A diagnosis of idiopathic gigantomastia, type 1b (non-obesity associated) was thus contemplated and patient underwent bilateral reduction mammoplasty after informed consent. Breast meridian, inframammary fold, midline, breast tangent and wise-pattern markings were marked bilaterally. Superomedial pedicles were marked and dissected along with respective nipple areolar complex (NAC). Excess skin and breast tissue were removed from the lower medial, inferior and lateral quadrants, which amounted to 4500 gm in the right and 3000 gm in the left breast (Fig. 1b). NACs based on superomedial pedicles were later inserted into their respective new positions and skin was closed in layers. Postoperative period was uneventful and the patient had marked improvement in self-perception of body image, as well as physical and psychological comorbidity. There was no regrowth of breast tissue on follow-up after 1 year (Fig. 1c).

Case 2

A 30-year-old multiparous female presented with excessive breast enlargement and ulcers for the past 5 years. She was on levothyroxine for subclinical hypothyroidism. There was no chronic drug intake or evidence of autoimmunity, including negative TPO. On examination, her BMI was 38.4 kg/m^2 following a weight gain of 9 kg in the past 1 year. She attained menarche at the age of 12 years and had regular cycles. She had two children, 12 and 10 years old, and had breastfed both for a year each. There was no history of gigantomastia during both pregnancies. On examination, sternal-nipple distances were 30 and 28 cm (right and left) and nipple-inframammary fold distances were 14 and 15 cm (Supplementary Fig. 1). No nodules were palpable. Her hormonal profile was normal with LH/FSH—7.7/6.2 IU/L, 17-β E2 of 36 pg/ml, testosterone 0.5 nmol/l, DHEAS 145 µg/dl, progesterone of 0.8 ng/ml and prolactin of 4.3 ng/ml. TSH on treatment was 2.8 mIU/l with fT3 of 2.84 pg/ml and fT4 of 1.4 ng/dl. Hba1c was 4.6% and HOMA-IR was 2.8. Serum autoantibodies and tumour markers were normal. Other investigations revealed non-alcoholic fatty liver disease and dyslipidemia. Mammogram was normal. Core biopsy of both breasts showed normal breast parenchyma without any evidence of malignancy. A diagnosis of idiopathic gigantomastia 1a (obesity related) was made. She was offered reduction mammoplasty, but she declined surgery. Hence, she was advised lifestyle modification, breast support and was managed medically for comorbidities.

Case 3

A 56-year-old female, postmenopausal for the past 10 years, having delivered her youngest child 32 years back, presented with enlargement of both breasts for the past 5 years leading to a restriction of routine activities. She had two uneventful pregnancies and breastfed both her children for 6 months. Her BMI was 30 kg/m^2 and breast examination revealed diffusely enlargement without lumps, ulcers (Supplementary Fig. 2) or galactorrhoea. Mammogram was within normal limits except a solitary right axillary node 1× 1 cm. Her hormonal profile was within normal limits, 17—βE2 26 pg/ml, testosterone 0.6 nmol/l, DHEAS 92 µg/dl, prolactin 19 ng/ml, IGF1 132 ng/ml (54–208) and FSH of 50 IU/L in accordance with her postmenopausal status. Thyroid hormones were normal (fT3—3.2 pg/ml, fT4—0.9 ng/dl, TSH—1.73 mIU/l). TPO and other autoantibodies were negative. She also had non-alcoholic steatohepatitis. Again, a diagnosis of idiopathic gigantomastia, type 1a (obesity related) was made. Patient was offered mastectomy, but she refused the same. Core biopsies revealed fibroadipose and fibrocollagenous tissue without any neoplastic changes. Patient was counselled about diet and physical activity and prescribed ursodeoxycholic acid.

Immunohistochemistry and Immunofluorescence

This was a retrospective analysis and written informed consent was obtained from all individual patients included in the study. For case 1, specimen of surgical pathology and for cases 2 and 3, core biopsy specimens were subjected to hematoxylin and eosin staining, as well as ER, PR and Her-2neu immunohistochemistry. Paraffin-embedded sections (4-µm thickness) were deparaffinised followed by rehydration with decreasing dilutions of ethanol. Antigen retrieval was done by trypsin (0.05%) followed by incubation for 1 h in blocking buffer [5% Normal Goat Serum (Vector Laboratories, UK)]. Overnight incubation with the primary antibodies anti-PDGFR-α (Santa Cruz; sc-398206; 1:100)/β (Santa Cruz SC-432; 1:100), anti-aromatase (ab 18995; 1:100), anti-IGF1(ab 9572; 1:100), anti-IGF2 (ab 177467; 1:100), anti-PTHrP (ab224503; 1:100), anti-EGFR (ab52894; 1:200), anti-TGF-β (ab92486; 1:100) and anti-PRL (1:300) antibodies was followed by 1 h incubation with a secondary goat anti-mouse antibody (Vector

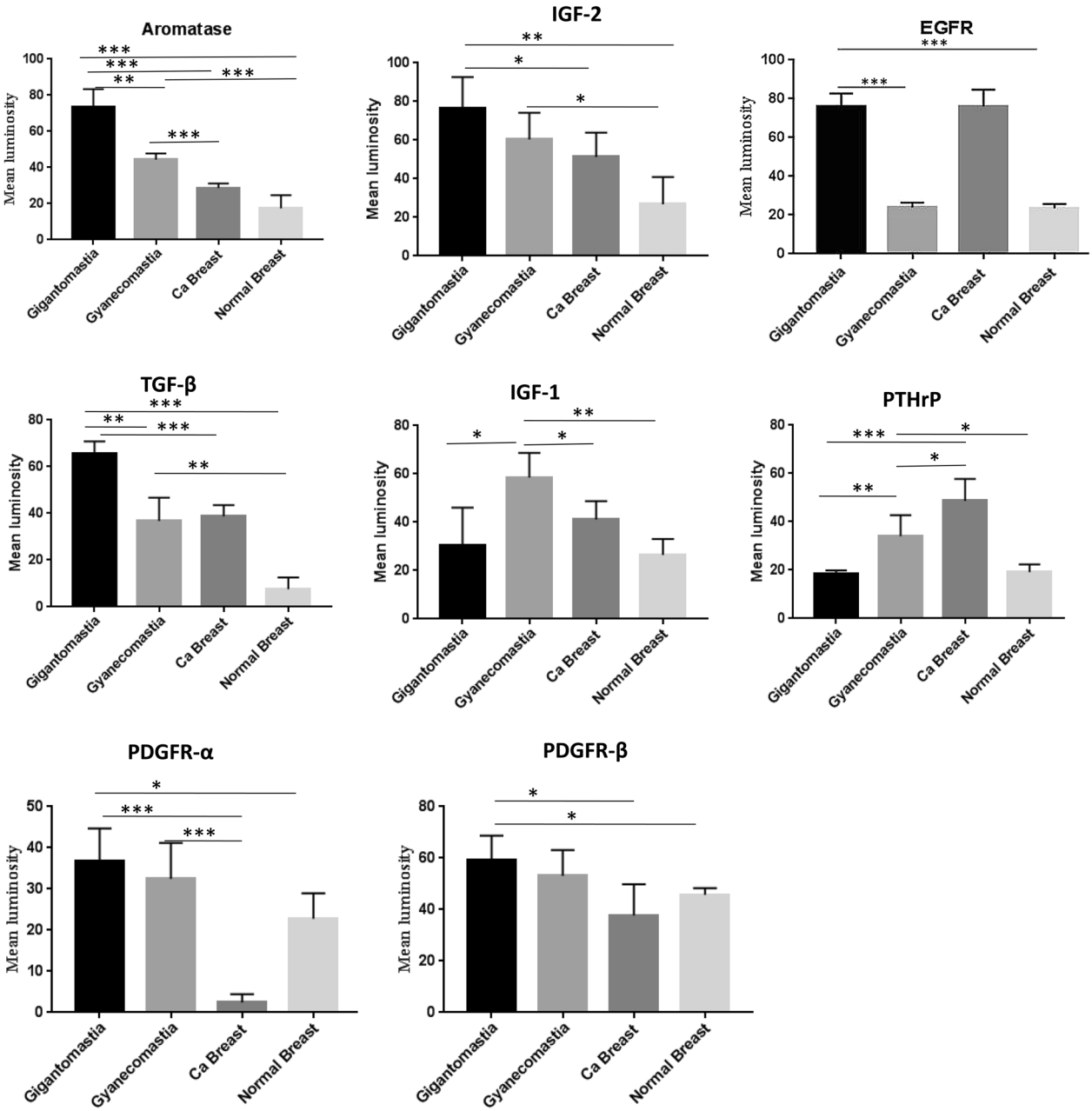

Fig. 2 Analysis of IF sections imaged in three positions and quantified for mean pixel luminosity of markers aromatase, EGFR, TGF-β, PTHrP, IGF-1, IGF-2, PDGFR-α and PDGFR-β. It demonstrates a significant increase in aromatase, TGF-β, IGF-2, PDGFR-α and PDGFR-β in gigantomastia. Note significantly lower luminosity of EGFR, PTHrP and IGF1 in patient samples. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

Laboratories; BA-9200; 1:300). This was followed by DyLight 549 Streptavidin (Vector Laboratories; SA-5549; 1:300) in order to detect PDGFR-α and PRL and 1 hour incubation with a secondary DyLight® 488 anti-rabbit IgG (Vector Laboratories; DI-1488; 1:300) for all other markers. Cell nuclei were stained with DAPI [4′,6-diamidino-2-phenylindole (VECTASHIELD Antifade Mounting Medium with DAPI; H-1200)]. Images were acquired using an immunoflouroscence microscope (EVOS, Thermo Fisher scientific) and the mean pixel luminosity of the staining was calculated using Adobe Photoshop CS6. IF quantification of hormones and growth factors in relation to normal, benign and malignant breast pathology is provided in Fig. 2.

Statistical analysis

Statistical analysis was performed using Graphpad Prism 7.0 (San Diego, CA). For two group comparisons to analyse

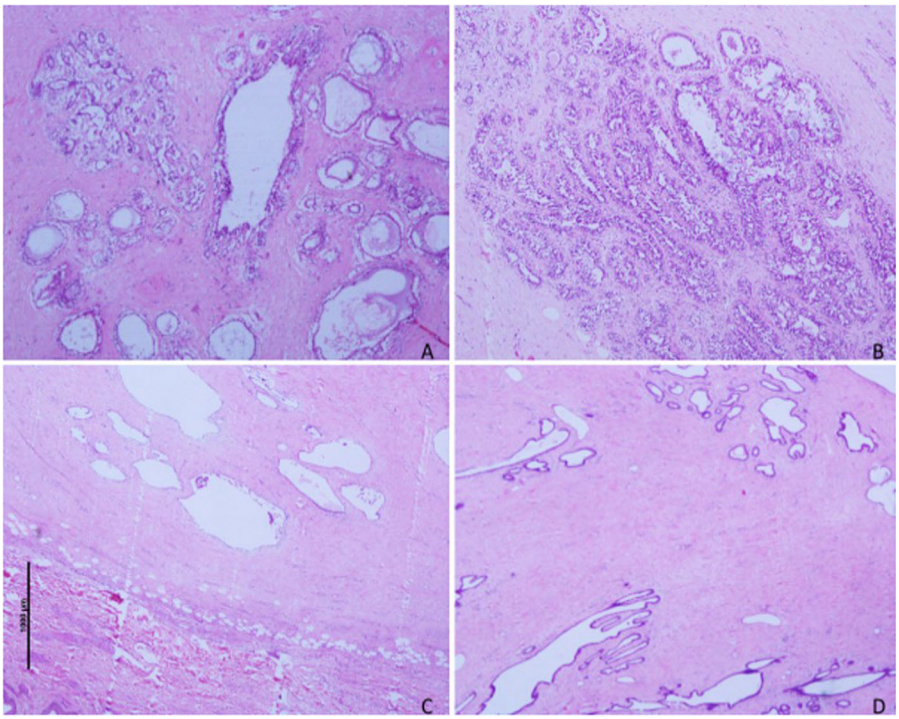

Fig. 3 Panel of representative microphotographs of the breast mass showing (**a**) Replacement fibrosis of the breast parenchyma by densely collagenised tissue. There is cystic dilatation of the terminal ducts and remnant lobular acini, some containing secretion. **b** Similar changes to **a** but showing mild focal adenosis. **c** Low power view showing the well circumscribed mass with cystic dilation of the lacteals. The section was taken from the superficial aspect with the overlying skin which can be seen at the left lower corner. **d** Focal papillary fronds depicting the papillary like infoldings of the stroma mimicking a benign phylloids tumour

differences between tissues, student's *t*-test was used. In all instances, data were expressed as means ± SE. A p-value < 0.05 was considered significant and that <0.01 was considered as highly significant.

Results

In all three cases, the consistent histopathological finding was increased fibroadipose and fibrocollagenous tissue with dense collagen but without any evidence of malignancy. The ductal compartment showed cystic dilatation of terminal ducts with a variable degree of replacement fibrosis. Foci of epithelial proliferation arranged in papillary fronds, as well as focal mild adenosis resembling phylloides tumour, were also noted (Fig. 3). Immunohistochemistry with ER, PR, Her-2neu and prolactin immunostaining performed in two of the biopsies showed positive staining for ER and PR in the dilated and sclerotic epithelial cells lining the lobular and terminal ducts. Her-2neu was focally positive in only one of the biopsies, while prolactin was negative in all the cases (Fig. 4).

Immunofluorescence for various hormones and growth factors was performed on the patient samples vis-à-vis normal breast tissue, abnormal benign breast tissue (gynecomastia) and infiltrating ductal carcinoma breast. Representative images of patient tissues with corresponding gynecomastia and carcinoma breast samples are shown in Figs. 5–10 and Supplementary Figs. 3 and 4. Appropriate positive and negative controls were examined. Aromatase was found to be 4.2-fold upregulated in gigantomastia as compared with normal breast, 1.6-fold as compared with gynecomastia and 2.6-fold upregulated as compared with breast carcinoma, with all values being significant ($p <$ 0.05). Overexpression of IGF-2, EGFR, TGF-β, PDGFR-α and PDGFR-β was also demonstrated in gigantomastia. IGF1 and PTHrP expression was significantly lower in gigantomastia.

Discussion

The cases enlisted above depict the wide clinical spectrum of idiopathic gigantomastia (IG) with a common pathologic signature in the form of overexpression of aromatase, EGFR, IGF2, TGF-β, PDGFR-α and β and underexpression of PTHrP, a key hormone implicated in breast enlargement during pregnancy. Hence, it can be postulated that PTHrP causes gestational gigantomastia but has only a minor role in idiopathic gigantomastia.

The exact definition of gigantomastia still eludes clarity but some consensus exists in terms of the amount of excess breast tissue that is removed during surgical intervention, arbitrarily taken as 1500 gm [5]. Others have used definitions including size of brassiere (D cup) or breast tissue exceeding 3% of total body weight [6]. More than a hundred cases of gigantomastia have been described in the literature in one of the largest reviews on this subject [5] with 85% cases being either "virginal" (pubertal onset) or "gestational" (pregnancy onset). The other causes include

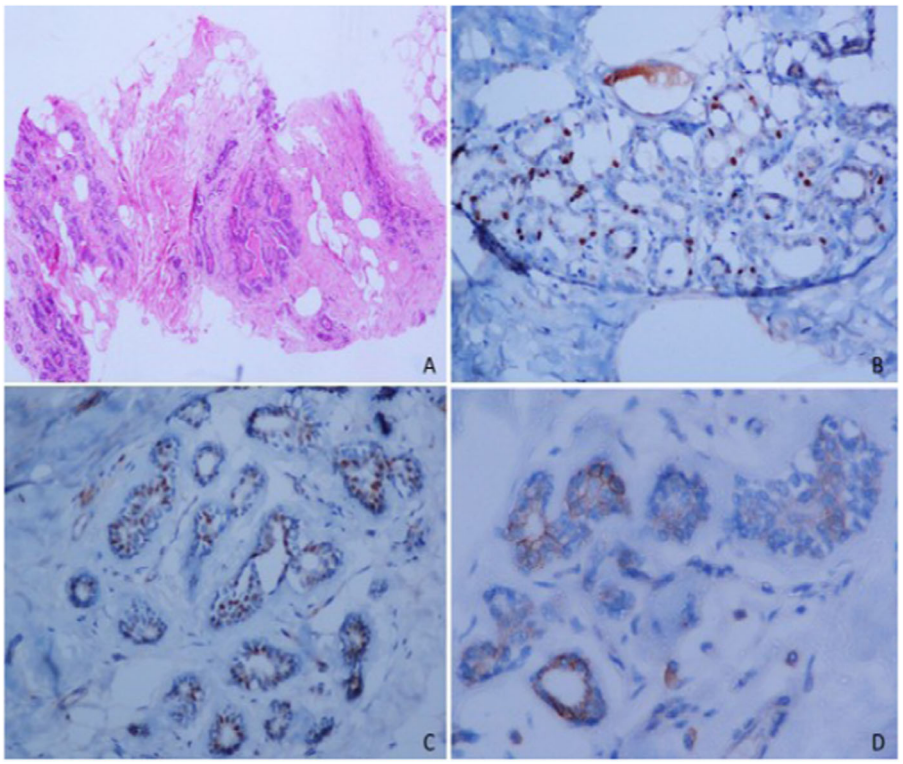

Fig. 4 Panel of microphotographs showing (**a**) low power view of the whole true cut biopsy that was received showing extensive inter and intralobular fibrosis. Panels **b–d** highlight the immunohistochemistry staining. **b** ER positive lobular cells. **c** The PR positive lobular and terminal duct lining epithelial cells. **d** The very occasional Her-2neu positive epithelial cells

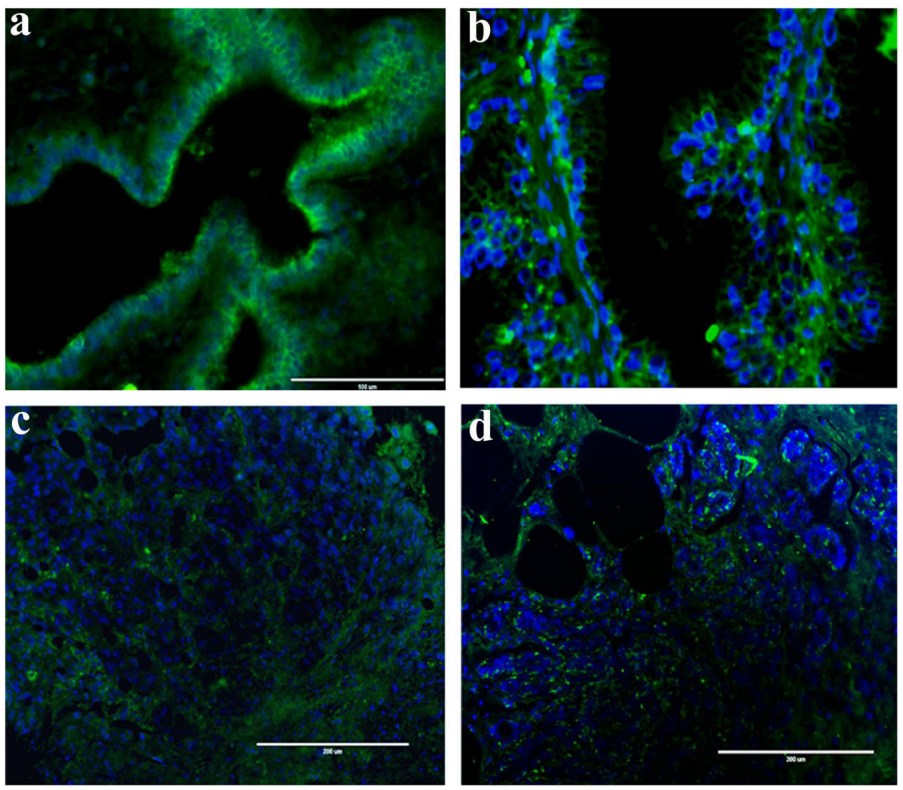

Fig. 5 Immunofluorescence staining of aromatase in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. The sections show overexpression of aromatase in gigantomastia tissue. Scale bar: 100 µm

drug-induced (penicillamine, cyclosporine and bucillamine), autoimmunity associated [7], tumours and syndromes. However, idiopathic gigantomastia is a rare entity, and as proposed, is divided into type 1a (BMI > 30 kg/m^2), type 1b (BMI < 30 kg/m^2), type 2a (puberty related), type 2b (pregnancy related) or type 3 (drug related) [5]. The

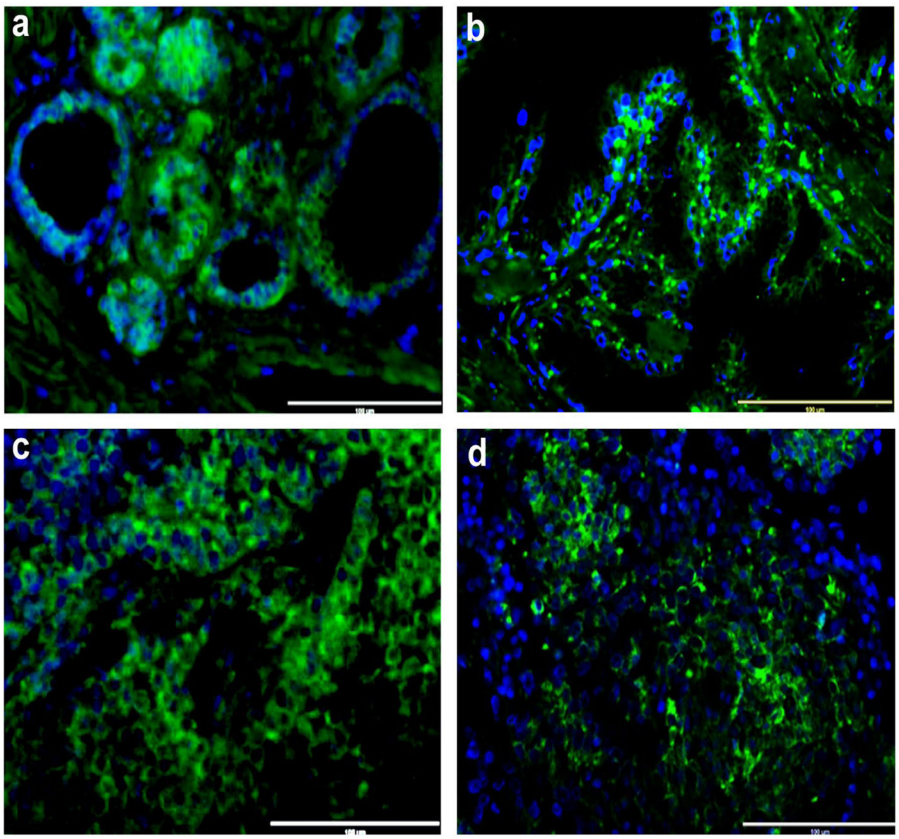

Fig. 6 Immunofluorescence staining of IGF2 in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. The sections show overexpression of IGF2 in gigantomastia tissue. Scale bar: 100 µm

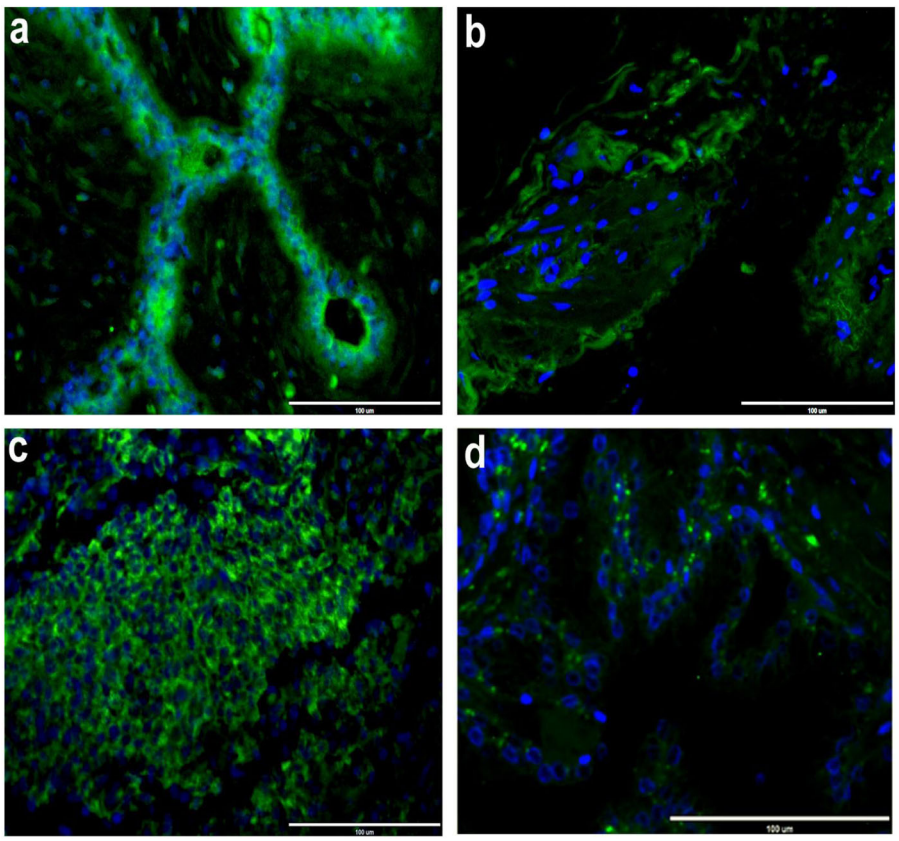

Fig. 7 Immunofluorescence staining of EGFR in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. The sections show overexpression of EGFR in gigantomastia tissue. Scale bar: 100 µm

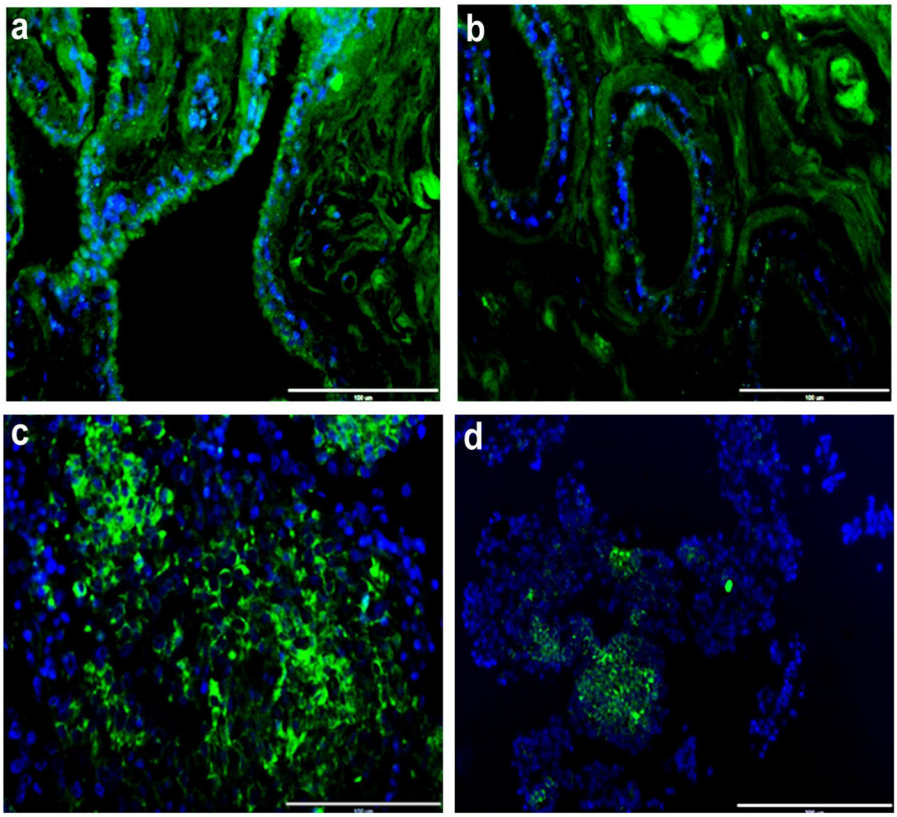

Fig. 8 Immunofluorescence staining of TGF-β in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. The sections show overexpression of TGF-β in gigantomastia tissue. Scale bar: 100 µm

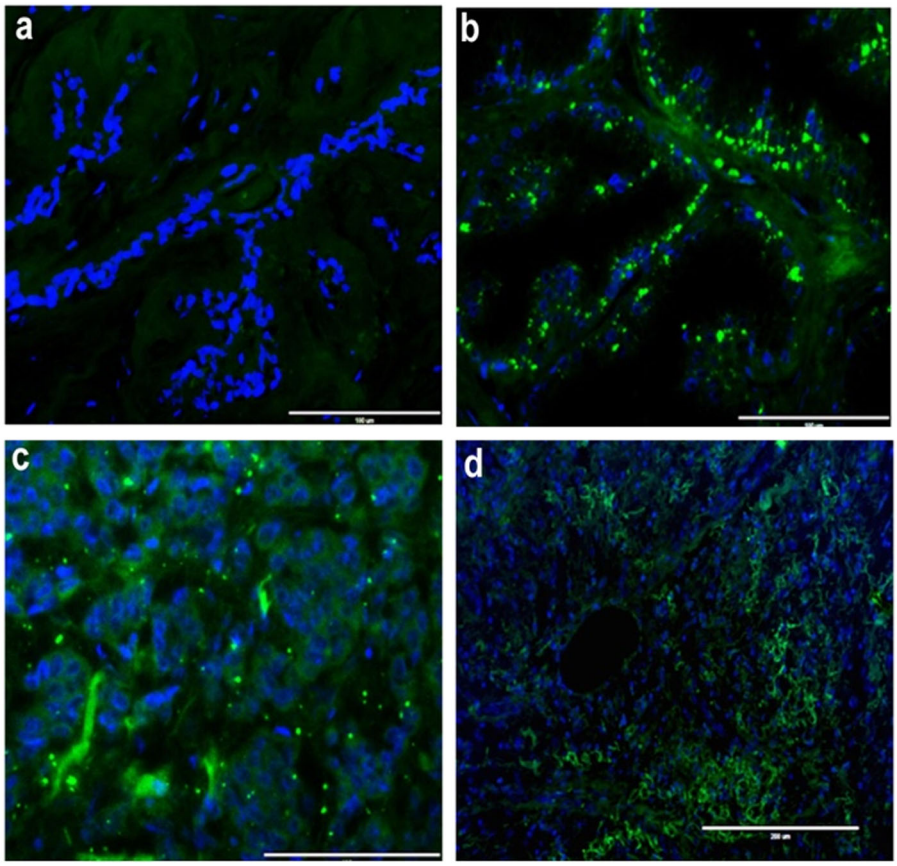

Fig. 9 Immunofluorescence staining of PTHrP in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. Scale bar: 100 µm. The sections show underexpression of PTHrP in patient tissues

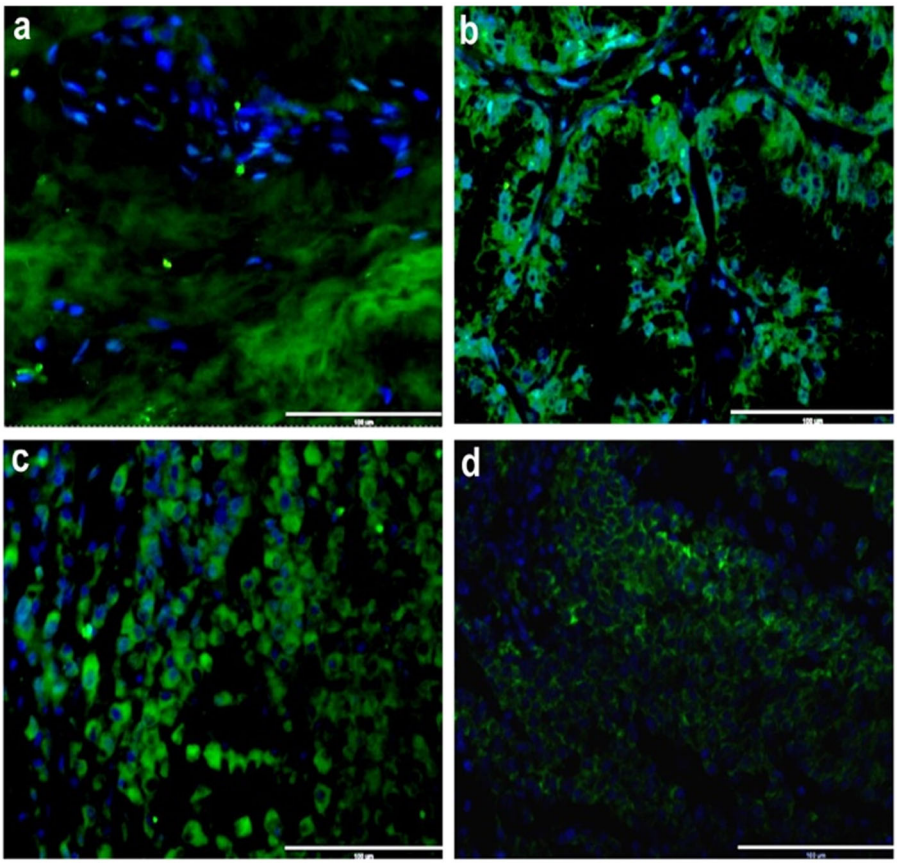

Fig. 10 Immunofluorescence staining of IGF1 in gigantomastia (**a**), gyanecomastia (**b**), breast carcinoma (**c**) and normal breast (**d**). Sections were counter stained with DAPI. Scale bar: 100 µm. The sections show underexpression of IGF1 in patient tissues

presentation of IG can occur at any age, as well depicted by our three patients. Pain and discomfort in the breasts, ulceration, back pain, difficulty in sleeping and loss of nipple sensation are some of the common complaints. The social, emotional and psychological impact of this condition are also enormous with deranged body image perception and impaired quality of life [8]. A Pubmed/MEDLINE search for the terms "idiopathic gigantomastia" and "idiopathic macromastia" showed only a handful of cases, which are summarized in Table 1.

The human breast is an endocrine target organ for multiple hormones, growth factors and cytokines. About two-thirds of breast malignancies are hormone-dependent [9], offering proof of the fact that breast neogenesis is heavily dependent on a functional endocrine machinery. However, while normal breast development is dictated by circulating hormones, it is the paracrine effects of these hormones that have a more important role to play in patients with apparently idiopathic gigantomastia. This was amply substantiated by immunofluorescence performed in tissue samples of our patients with IG with normal circulating hormonal levels in all. Further, occurrence of IG in a postmenopausal woman strengthens the fact that the paracrine milieu is more pivotal than circulating hormones in causing gigantomastia.

Embryonic breast development is mostly directed by the mesenchyme while peripubertal ductal morphogenesis, pregnancy related lobulo-alveologenesis and menopausal involution all depend upon hormones and growth factors. Following allometric growth pre-pubertally, estrogen, promotes proliferation of the ductal tree and terminal end buds [10, 11] by acting on stem cells located in epithelial niches. This is done in conjunction with local and systemic IGF1. Estrogen also induces the development of amphiregulin (a member of the EGF family), which, in turn, mediates its paracrine actions. Immunofluoresence in our patient samples showed significantly upregulated aromatase (>4-fold) leading to a hyperestrogenic milieu and causing massive epithelial proliferation. However, the relatively sparse ER expression in our patients, as shown by other studies as well, [12] raises a strong contention that paracrine effects of estrogen (mediated through EGFR) are more important in causing gigantomastia. Further, the observation that EGFR in our patient samples was significantly higher than normal breast tissue, lends credence to this fact.

IGF-2 is produced by stromal cells of the breast, whereas its receptors are present on the epithelial cells, demonstrating stromal-epithelial interactions. It promotes Cyclin D1 expression and regulates cell survival by modulating ER-β in a paracrine fashion. It is imperative to note that ER-

Table 1 PUBMED review of clinical characteristics and management strategies in cases of idiopathic gigantomastia

Year	Author	Age (years)	BMI (kg/m2)	Weight of excised breast tissue (kg)	Management procedure	Histopathology features	Adjuvant treatment
1994 [19]	Koger	31	NK	4.4	BBR	NK	NK
2002 [20]	Skillman	36	NK	12	Mastectomy	Nodular proliferation of glandular tissue, edematous fibrous stroma, focal lactational change	Goserelin 3.6 mg single dose
2003 [21]	Chrominski	51	NK	9	BBR	Fibroglandular tissue, lymphocytic infiltration, venostasis	None
2006 [22]	Kulkarni	36	NK	12	Redo-surgery for excision of recurrence	NK	Tamoxifen (4 months) before redo surgery
2006 [5]	Dancey	38	32	3	BBR	NK	NK
2006 [5]	Dancey	NK	33	3.1	BBR	NK	NK
2006 [5]	Dancey	56	30	3.1	BBR	NK	NK
2006 [5]	Dancey	28	22	3.2	BBR	NK	NK
2006 [5]	Dancey	44	29	3.2	BBR	NK	NK
2006 [5]	Dancey	55	34	3.5	BBR	NK	NK
2015 [23]	Cho	43	25.7	7.6	BBR	Nodular proliferation of tubules, epithelial and myoepithelial cells, 10% epithelial cells with positivity for estrogen and progesterone receptors	None
2015 [24]	Roy	40	NK	8.3	BBR	Pseudoangiomatous stromal hyperplasia (PASH) and giant fibroadenoma	None
2016 [25]	Oppenheimer	29	NK	NK	Mastectomy f/b reconstruction	PASH, Phyllodes tumour	None
2016 [26]	Barragan	11	19.5	4	BBR	Hyperplastic terminal lobules with edematous stroma; ER/PR –ve	None
2019	Index patient 1	35	28.4	9	BBR	Fibroepithelial lesion with myoepithelial cells and stromal component having spindle cells, negative panCK staining,	Intermittent Danazol intake prior to surgery; None after
	Index patient 2	30	38.4	ND	Non-surgical	Fibroadipose proliferation ER-ve; PR 5% positive	Weight reduction
	Index patient 3	56	30	ND	Non-surgical	Fibroadipose and fibrocollagenous tissue with ducts; no hyperplasia	Weight reduction, Urseodeoxycholic acid

β is widely distributed in all compartments of the breast, while ER-α is localised to the epithelium. Immunofluorescence in IG tissue of our patients showed upregulated IGF2 thereby proving its dominant role in gigantomastia. The importance of IGF2 in causing gigantomastia is proved by the fact that Beckwith–Wiedemann syndrome, a disease of IGF2 overexpression, is associated with gigantomastia. However, none of our patients had manifestations of this syndrome, thereby demonstrating that local upregulation of IGF2 is the reason for gigantomastia alone, without systemic features. IGF2 has also been documented in fibroadenomas and phyllodes tumours [13]. Hence, IGF2 upregulation provides an important mechanistic insight into the etiopathogenesis of gigantomastia, with limited role in normal breast development but profound effects in gigantomastia.

TGF-ß, an important cytokine, regulates breast morphogenesis by upregulating PDGF, which then acts via PDGFR-α and PDGFR-β. TGF-ß IF in patient IG tissue showed highest levels compared with other samples. PDGFR-α and PDGFR-β were also found to be higher in IG tissue. TGF-ß is often implicated in fibrotic transformation and the prominent fibroadipose and fibrocollagenous content found on histopathologic examination of our patients is proof of its important role in IG.

IF results showed underexpression of PTHrP and IGF1 in patient samples. PTHrP regulates mesenchyme specification, epithelial-mesenchyme interaction and ductal and nipple growth [14]. Immunoperoxidase techniques have demonstrated upregulated PTHrP in gestational gigantomastia of gestational onset. But, no comparative quantification with respect to normal breast and other benign or malignant breast diseases was performed in that study [15]. PTHrP expression in our patient samples, however, was lower, implying its limited role in IG. Also, PTHrP mediated gestational gigantomastia has been successfully reversed after caesarean section alone, with persisting gigantomastia, thereby establishing placenta, rather than breast, as an important source of this hormone [16].

IGF-1 mediates the action of GH on the breast and is permissive for both estrogen and progesterone. It slow levels in tissue again proves its limited role in etiopathogenesis of IG. Prolactin is the principal lactogen but its role in breast neogenesis is shown by the fact that gigantomastia has been found to be associated with macroprolactinemia in upto 10–25% of patients [17]. However, the mean luminosity of prolactin was negative in all our cases, again proving its role in normal pregnancy and lactation but a limited role in the development of gigantomastia.

Overall, there is an indisputable role of endocrine, immune and growth factors in normal development of the mammary gland with ample evidence suggesting that local concentrations and actions of these factors might be more important than their systemic levels as we hypothesised and later proved.

Management of gigantomastia depends on factors like age of the patient, parity, future pregnancies, underlying cause if any, and wish of the patient concerned. Except the drug induced cases that may be reversible, almost other patients need a definitive treatment modality. Medical agents that have been tried include selective estrogen receptor modulators, progesterone, glucocorticoids (prednisone, dexamethasone) especially in autoimmune cases, dopamine agonists (bromocriptine) in gestational cases, danazol and diuretics in patients with idiopathic gigantomastia, but with dismal results. Surgical management is the mainstay of therapy for gigantomastia, provided the patient is willing for the same, with significant relief not only in terms of restoration of anatomy, resolution of pain and discomfort but also in psychological parameters and sexual function [18].

The limitations of our study include non-estimation of serum levels of IGF2 and PTHrP. However, none of our patients had evidence of overgrowth or hemihypertrophy or hypercalcemia, thereby proving that these serum levels were probably normal. The analysis was carried out in only three patients and needs to be confirmed in a larger sample. But, comparative immunofluorescence quantification with other normal and pathological breast tissues adds to the strength of our findings.

Conclusion

Idiopathic gigantomastia can have a varied spectrum. It is a diagnosis of exclusion as proved by development unrelated to puberty or pregnancy, normal hormonal levels, autoimmune profile and tumour markers. Hence, it is conceivable that there is a hypersensitivity to the paracrine milieu of upregulated aromatase, EGFR, IGF2, TGF-β, PDGFR-α and β and due to locally upregulated expression. Further research to elucidate the exact endocrine and paracrine factors and their downstream pathways is the way ahead.

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Author contribution L.D. drafted the manuscript and interpreted observations. A.R. was involved in histopathology interpretation and manuscript writing. K.V. was involved in histopathology interpretation and manuscript editing. A.G. assisted surgery of the first case. S.M. assisted surgery of the first case. A.B. edited the manuscript. P.D. conceived the idea and was involved in manuscript writing as well as editing. S.S.T. operated the case and was involved in manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed involving human participants/patients were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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