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COMMENTARY

The role of expression of estrogen and progesterone receptors in idiopathic gynecomastia etiology

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Gynecomastia is a benign enlargement of the male breast. If the etiology of breast enlargement remains unknown, gynecomastia is considered as idiopathic, and its frequency is estimated from 25% to 61%. Studies on the etiology of idiopathic gynecomastia involved examination of the level of the following hormones in blood: human prolactin, thyroxin, cortisol, human chorionic gonadotropin (β-hCG), leptin, growth hormone and insulin-like growth factor (IGF) and of receptors for estradiol, androgens, β-hCG, prolactin, and luteotropin in the tissue of men's mammary glands.[1–4] The studies showed that these factors may play a role in the pathophysiology of gynecomastia. However, their results are inconsistent. There are also some analyses which pointed out that a microsatellite polymorphism in the CYP19 gene can cause gynecomastia.[5] The aim of this research was to examine the receptor status of estrogen (ER) and progesterone (PR) receptors of breast tissue in men with idiopathic gynecomastia and to verify the hypothesis concerning ER and PR overexpression in idiopathic gynecomastia.

The study involved 46 patients who underwent beast reduction due to the idiopathic form of gynecomastia in years 2010-2017. The average age of the studied individuals was 26.6 years (SD = 8.2; range 17-51). All of the patients had undergone endocrine (testosterone, estradiol, prolactin, luteinizing hormone, hCG, thyroid-stimulating hormone, liver function tests) and, if needed, genetic examinations (karyotype) and a detailed medical interview had also been taken. All had breast and, if needed also testes ultrasonography examination done. Surgical techniques included subcutaneous mastectomies performed through a periareolar incision or mastectomies with skin reduction. Histopathological examinations of the removed tissues are done routinely. Tissue samples for the examination of receptors were obtained after a histopathological analysis. Estrogen receptors (ER) and progesterone receptors (PR) expression was detected immunohistochemically. The slides were loaded on the Dako AutoStainer Plus (Dako) and incubated with primary "ready to use" ER and PR antibodies according to the instruction of a manufacturer. As a positive control, the sections from ER and PR positive breast carcinoma were used. ER and PR positive nuclei were evaluated using a computer image analysis system consisting of a PC computer equipped with a Pentagram graphic tablet, Indeo Fast card (frame grabber, true-color, real-time), produced by Indeo (Taiwan), and a color TV camera Panasonic (Japan) coupled with Carl Zeiss microscope (Germany). This system was programmed (MultiScan 18.03 software, produced by Computer Scanning Systems, Poland) to calculate the number of objects (semiautomatic function) (Figures 1 and 2). The results were presented as a percent of positive nuclei of all nuclei counted in glandular epithelium. The protocol for the study was approved by the local ethics committee (RNN/191/17/KE).

The mean age of the onset of gynecomastia was 13.9 years (SD = 1.5 years). All patients with idiopathic gynecomastia exhibited

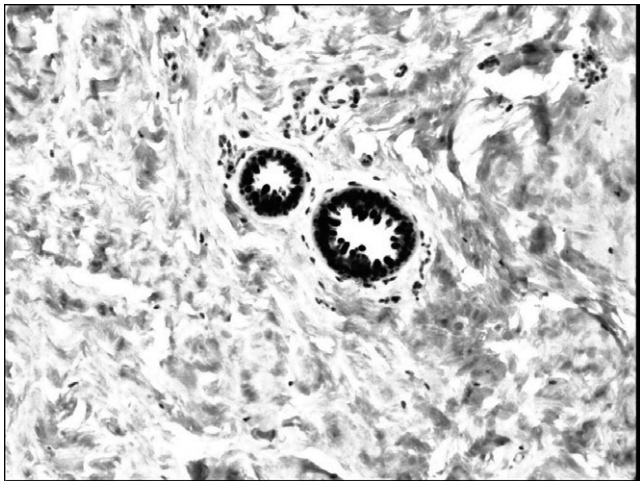

FIGURE 1 Immunohistochemistry. Highly positive expression of ER in nuclei of glandular epithelium. Magn. 200x

positive estrogen and/or progesterone expression in the breast tissues removed during surgery (Table 1). It was found out that most glands had ER expression ranged 61%-90% (21 specimens) or 91%-100% (n = 13), while the rest 31%-60% (n = 9) or 0%-30% (n = 3).

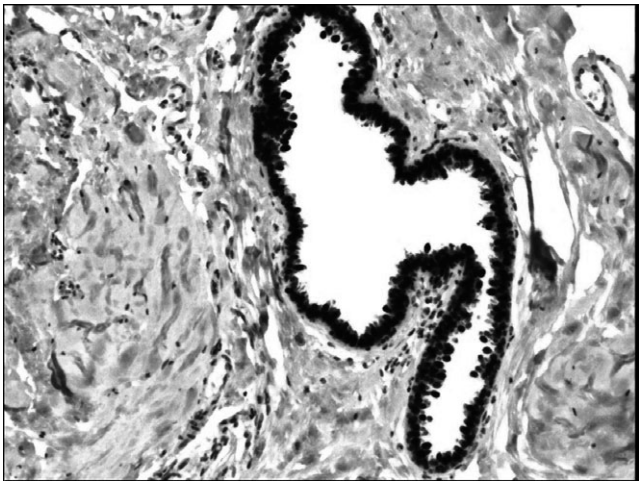

FIGURE 2 Immunohistochemistry. Highly positive expression of PR in nuclei of glandular epithelium. Magn. 200x

The most common PR expression ranged 31%-60% (n = 21) and 61%-90% (n = 15). Nine glands exhibited PR expression ranged from 0% to 30% and one 91%-100%. Statistical analysis did not reveal any correlations between ER and PR expression and: the stage of gynecomastia according to Simon ($P = 0.46$, $P = 0.38$), patients' age ($P = 0.9$, $P = 0.28$), the age of gynecomastia onset ($P = 0.23$, $P = 0.46$) and the side of gynecomastia ($P = 0.055$, $P = 0.26$).

The results revealed that all glands in men with idiopathic gynecomastia exhibited positive ER and/or PR expression. Moreover, in 34/46 samples ER expression was positive in >60% nuclei and in 37 glands PR expression was at least moderate (>30%). Similar results were obtained by Sasano et al (1996) who found that ER and PR expression was observed in the nuclei of ductal cells in all 30 cases of idiopathic gynecomastia. Moreover, the expression was also high or moderate.[6] Ferreira et al (2008) also found positive expression (>10% nuclear immunoreactivity) of ER and PR in all analyzed 30 cases of gynecomastia. However, the authors did not present clinical data concerning gynecomastia (idiopathic or pathological) and did not specify the percentage of cells that were ER and PR immunoreactive.[7] Pensler et al (2000) found out that none of the patients with adolescent breast enlargement demonstrated significant elevation of ER and PR, contrary to those with

TABLE 1 Estrogen and progesterone receptors expression (%) in idiopathic gynecomastia patients

No	Age of surgery	Age of onset	Simon stage	side	ER	PR	No	Age of surgery	Age of onset	Simon stage	side	ER	PR
1	18	13	IIa	B	60	60	24	17	14	IIb	B	80	60
2	21	14	IIa	B	90	80	25	22	14	IIa	B	90	80
3	31	14	I	B	80	20	26	30	13	IIb	B	70	90
4	34	13	III	B	20	15	27	33	14	IIa	B	90	70
5	32	15	IIb	B	80	50	28	24	13	IIa	B	80	80
6	19	12	I	B	95	80	29	34	13	IIb	B	90	60
7	23	13	IIa	B	50	15	30	20	14	III	B	95	50
8	27	16	IIa	B	90	30	31	22	14	IIb	B	90	50
9	19	15	IIa	B	60	0	32	24	13	IIa	L	20	10
10	25	18	IIa	L	70	70	33	20	12	IIa	B	90	50
11	23	13	IIa	B	100	90	34	31	14	IIb	B	95	90
12	19	14	IIa	B	80	60	35	35	14	IIa	B	100	90
13	20	14	III	B	100	90	36	18	13	I	B	60	40
14	34	30	I	L	60	50	37	42	14	IIb	B	90	75
15	20	12	IIb	B	90	60	38	28	15	IIa	R	40	10
16	51	40	IIa	B	100	90	39	22	16	I	B	20	20
17	19	13	IIa	B	100	60	40	28	14	IIa	R	60	60
18	18	13	I	B	90	75	41	39	15	IIb	B	70	40
19	18	13	IIa	B	100	40	42	24	13	IIb	B	95	60
20	29	20	IIa	B	80	60	43	23	14	IIb	B	90	50
21	19	11	I	B	50	40	44	46	14	IIa	B	50	30
22	19	14	I	B	90	40	45	40	13	IIb	B	100	100
23	27	13	IIa	B	95	60	46	36	14	IIa	R	100	70

B, bilateral; ER, estrogen; L, left; PR, progesterone; R, right.

Klinefelter syndrome[8] Similar results were presented by Lee et al (1990) who studied breast tissue removed from seven boys of age 16-17 years without hormonal disturbances. Estrogen receptors were not detectable in any of the examined breasts, while progesterone receptors were detectable at a low level only in two patients.[9] We can assume that the authors may have described the profile of receptors in a physiological condition—adolescent gynecomastia. In our study, we examined adult men with pathological condition—idiopathic gynecomastia. In our earlier study concerning the etiology of gynecomastia, we found out that prenatal estrogen and testosterone exposure may be a causative factor of idiopathic breast enlargement.[10] To conclude, the obtained results may indicate that men with idiopathic gynecomastia present primary "overexpression" of ER and PR This thesis may be supported by the fact that in many cases of idiopathic gynecomastia antiestrogens appear to be effective in an unknown mechanism. Additionally, these findings may pave the way for further researches on effective pharmacotherapy in this condition and explain a mechanism of its efficacy.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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