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Alopecia in a premenopausal breast cancer woman treated with letrozole and triptorelin

A 37-year-old premenopausal woman with relapsed breast cancer (BC) in the right supraclavicular nodes, after failed treatment with the combination luteinizing hormone releasing hormone-a (LHRHa; triptorelin) plus tamoxifen, was started on triptorelin 3.75 mg every 28 days plus letrozole 2.5 mg daily. Approximately 6 months after starting this therapy, she complained of a daily scalp hair loss while combing and progressively developed a diffuse non-scarring alopecia on her crown. There were no signs of virilization. A gynecological examination showed a normal looking vagina and uterine cervix. The uterus was normal in size and there were no ovarian masses at ultrasonography. Her previous medical history was unremarkable. She was not taking any other drug. Hematological parameters were normal. Blood examination ruled out pituitary or thyroid problems. There were no other possible causes that could induce alopecia, such as lupus erythematosus, HIV infection, secondary syphilis, or deficiencies of protein, iron, biotin or zinc (Table 1). A dermatologist prescribed topical minoxidil 2%, two local applications (2 ml) daily. Approximately 6–8 weeks after initiating minoxidil, hair loss stopped and hair regrowth became apparent.

Hormonal levels of premenopausal BC women treated with the association LHRHa plus an aromatase inhibitor (AI) are different from those of postmenopausal women treated with an AI alone [1]. Whether estradiol directly inhibits 5 α-reductase or whether the effect of estrogens might be explained by an increased conversion of testosterone to the weaker androgens, thereby diminishing the amount of testosterone available for the conversion to dihydrotestosterone (DHT), remains to be shown [2]. Additionally, aromatase levels have been demonstrated to be decreased in balding scalp [3]. This is the first report of alopecia related to the combination of LHRHa (triptorelin) with a non-steroidal AI. AIs alone lead to thinning hair, rather than baldness, with an incidence of 2.5–6%. One report suggested that LHRHa can also induce hair loss [4].

Consistent with the role of aromatase in avoiding androgen-mediated effects on androgen-dependent hair follicles is the observation that women taking AIs for the treatment of BC often experience androgenetic alopecia-like hair loss, as a consequence of the hormonal imbalance towards androgenization of the hair follicles. We could speculate that the LHRHa caused a fall in estradiol concentrations, leading to a relative hyperandrogenism. Additionally, the reduction of aromatase activity driven by letrozole may have resulted in a further relative increase in systemic

Table 1. Hormonal tests at the most recent follow-up visit

Hormonal test	Results	Normal values
LH (mUI/ml)	<0.5	follicular phase 1–18
		ovulation 24–105
		lutheinic phase 0.4–20
		post-menopausal status 16–82
		men 2–12
FSH (mIU/ml)	8.89	follicular phase 4–13
		ovulation 5–22
		lutheinic phase 2–13
		post-menopausal status 20–138
		men 1–8
17-β-estradiol (pg/ml)	<28	follicular phase 39–189
		ovulation 94–508
		lutheinic phase 48–309
		post-menopausal status <41
		men <77
Estrone (pg/ml)	29	follicular phase 37.2–137.7
		ovulation 58.9–229.0
		lutheinic phase 49.8–114.0
		menopausal status 14.0–103.0
		men 30–90
Progesterone (ng/ml)	0.17	follicular phase 0.15–1.40
		lutheinic phase 3.34–25.58
		menopausal status <0.73
		men 0.28–1.22
Testosterone (ng/ml)	0.30	women 0.14–0.76
		men 2.4–8.2
Androstenedione (ng/ml)	0.81	women 0.21–3.08
		men 0.30–3.10
		menopausal status 0.36–1.80
SHBG (nM/l)	35.8	women 51–111
		men 33–122
		pregnancy 220–450
Prolactin (ng/ml)	6.0	women 1.39–24.20
		men 1.61–18.77
Cortisol (ng/ml)	208.7	43–224
FT3 (pg/ml)	3.08	1.45–3.48
FT4 (ng/dl)	1.10	0.71–1.85

FSH, follicle-stimulating hormone; FT3, free tri-iodothyronine; FT4, free thyroxine; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

and pilosebaceous testosterone available for conversion to DHT. This synergic action may explain why our patient did not show alopecia while taking triptorelin with tamoxifen. Moreover, minoxidil lengthened and enlarged the small vellus hairs and decreased shedding, highlighting the hypothesis of a relative hyperandrogenism as the cause of alopecia. Female sex hormone-binding globulin (SHBG) levels are inversely correlated with the grade of alopecia [5]. In our patient, the SHBG levels were low, potentially due to the AI effect.

Considering the pivotal importance of pharmacological castration in premenopausal endocrine-responsive BC patients and the widespread use of AIs in the metastatic and, probably in the near future, adjuvant settings, potential alopecia should not be a determinant in making clinical decisions. However, oncologists must be aware of such atypical adverse events for treatment planning, in order to highlight its consequent distress and to provide psychological counseling, especially in young patients.

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References

1. Dowsett M, Doody D, Miall S et al. Vorozole results in greater oestrogen suppression than formestane in postmenopausal women and when added to goserelin in premenopausal women with advanced breast cancer. Breast Cancer Res Treat 1999; 56: 25–34.
2. Niiyama S, Happle R, Hoffmann R. Influence of estrogens on the androgen metabolism in different subunits of human hair follicle. Eur J Dermatol 2001; 11: 195–198.
3. Sawaya ME, Price VH. Different levels of 5 α-reductase type I and II, aromatase and androgen receptor in hair follicles of women and men with androgenic alopecia. J Invest Dermatol 1997; 109: 296–300.
4. Gateley CA, Bundred NJ. Alopecia and breast disease. BMJ 1997; 314: 481.
5. Vexiau P, Chaspoux C, Boudou P et al. Role of androgens in female-pattern androgenetic alopecia, either alone or associated with other symptoms of hyperandrogenism. Arch Dermatol Res 2000; 292: 598–604.

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Absence of chemotherapy-induced alopecia with paclitaxel in a case of hypothyroidism: case report

A 69-year-old woman presented in October 1998 with abdominal pain and distension. On physical examination, ascites and tenderness on palpating the lower abdominal area were found. An abdominal computed tomography (CT) scan revealed a 4.5 cm mass in the left ovary with multiple peritoneal implants and ascites. The serum tumor marker CA 125 was 190 U/ml (normal, <32), whereas thyroid hormones were within normal limits: thyroid-stimulating hormone (TSH) 5.1 U/ml, thyroxine 7.2 U/ml, triiodothyronine 1.2 U/ml.

She underwent a staging laparotomy and abdominal hysterectomy with bilateral salpingo-ophorectomy and omentectomy, stage IIIC disease was detected. Histology was consistent with serous cystadenocarcinoma grade 1–2. She received six cycles of chemotherapy with paclitaxel and carboplatin or cisplatin (alternate cycles). Toxicity was limited to grade 1 peripheral neuropathy with mild numbness in a glove-and-stocking distribution. No alopecia was evident at this point. At the end of chemotherapy, an abdominal CT scan showed complete radiological remission and serum CA 125 within normal limits.

One month later, she developed clinical signs of hypothyroidism, and TSH was 90 mU/l. On questioning, it appeared that the patient elected on her own to discontinue thyroxine replacement at the start of chemotherapy without informing the medical team. Thyroxine replacement therapy was recommenced and 2 months later thyroid hormones were within normal limits. As soon as thyroid function was restored, alopecia grade 2 appeared, 3 months after the completion of chemotherapy. Grade 2 alopecia was present for almost 2 months, after which hair regrowth was apparent.

Nine months later, the patient developed intra-abdominal relapse, and despite salvage treatment attempts, she died 3 months later from progressive disease.

The current case represents a very rare, probably unique, clinical entity. A possible explanation of the delayed onset of alopecia after the completion of paclitaxel chemotherapy could be attributed to the combined effects of thyroid hormones and chemotherapy upon the biological cycle of hair. Each hair follicle continually goes through three stages: anagen (growth), catagen (involution), and telogen (rest) [1]. Anagen is followed by catagen when hair follicles go through a highly controlled process of involution. Ultimately, the hair follicle enters the telogen stage when the hair shaft matures into a club hair which is eventually shed from the follicle [1]. The telogen stage lasts 2–3 months before the follicles re-enter the anagen stage and the cycle is repeated. At any given point, most of the hair follicles can be found in the anagen phase with only a small percentage in the telogen phase and just a few in the catagen phase (Figure 1).

Hair growth is influenced by many factors, including hormones, whose mechanism of action is not fully understood [2, 3]. Antineoplastic drugs disrupt the rapidly proliferating bulb matrix cells during the anagen stage. As a result, hair production ceases and the hair shaft becomes narrower with subsequent breakage and loss of hair; a phenomenon called anagen effluvium [4, 5]. Telogen effluvium is the excessive shedding of hair caused by an increased proportion of follicles entering the telogen stage. Low levels of thyroxine cause telogen effluvium [2].

In our clinical case, the patient was hypothyroid during chemotherapy with paclitaxel, due to the cessation of thyroxine replacement. As a result, most hair follicles probably entered the telogen stage (Figure 1). We hypothesize that paclitaxel could not act in the hair follicles that were in the telogen stage and thus no alopecia appeared (Figure 1). Once thyroid function was restored, it is likely that the telogen stage was completed leading to telogen