CASE & REVIEW

Permanent chemotherapy-induced alopecia: Case report and review of the literature

Ben Tallon, MBChB,[a] Elizabeth Blanchard, MD,[b] and Lynne J. Goldberg, MD[a]
Boston, Massachusetts

Reversible alopecia following chemotherapy is well recognized and typically not evaluated by dermatologists. However, there are an increasing number of reports of permanent chemotherapy-induced alopecia, typically following high-dose chemotherapy and subsequent bone marrow transplantation. We describe an unusual case of permanent alopecia in a patient who received adjuvant chemotherapy for breast carcinoma, and not a conditioning regimen before bone marrow transplantation. A unique histologic finding of replacement of anagen hair follicles by linear columns of basaloid epithelium is reported. We review the clinical and histologic findings of permanent chemotherapy-induced alopecia and speculate on its pathogenesis. (J Am Acad Dermatol 10.1016/j.jaad.2009.06.063.)

INTRODUCTION

Reversible alopecia following chemotherapy, or anagen effluvium, typically begins within 2 to 4 weeks after treatment onset, and hair grows back fully within 6 months.[1] Permanent alopecia occurring after chemotherapy is rare. The existing reports of permanent alopecia typically follow high-dose chemotherapy and subsequent bone marrow transplantation (BMT).[2-8] To our knowledge, there is only one recent report of permanent alopecia in the absence of BMT.[9] We describe a case of permanent hair loss following standard dose chemotherapy with docetaxel, carboplatin, and trastuzumab for the treatment of breast carcinoma and report unique histologic findings.

Abbreviations used:

AUC: area under the curve
BMT: bone marrow transplantation
CIA: chemotherapy induced alopecia
HDC: high-dose chemotherapy

CASE REPORT

A 72-year-old Caucasian woman with a history of ductal breast carcinoma presented with a complaint of persistent hair loss 13 months after completion of adjuvant chemotherapy. She had a history of invasive ductal carcinoma of the left breast associated with ductal carcinoma in situ. Following lumpectomy and sentinel lymph node biopsy, her final pathologic stage was T2, N0, MX, stage IIA estrogen receptor and progesterone receptor negative, with HER-2 overexpression confirmed by fluorescent in situ hybridization. Adjuvant chemotherapy was commenced with a regimen of docetaxel, carboplatin, and trastuzumab for 6 cycles every 3 weeks (weekly for trastuzumab), followed by trastuzumab every 3 weeks for the next year. Standard doses were used initially (docetaxel, 75 mg/m^2 = 150 mg; carboplatin area under the curve [AUC] 6 = 650 mg, and trastuzumab, 4 mg/kg = 380 mg). The trastuzumab was given according to a standard weekly dose of 2 mg/kg for cycles 2 to 5, then 6 mg/kg (500 mg) every 3 weeks to complete 1 year of therapy. Her first cycle was complicated by severe neutropenia with fever, vaginitis, fatigue, and dehydration, leading to removal of carboplatin from the regimen. Following her chemotherapy, she received radiation to the tumor bed with a total dose of 5940 cGy.

Two weeks after the start of her chemotherapy she began to lose the hair on her scalp, as well as her eyebrows, eyelashes, and body hair. By the completion of her chemotherapy, she was completely bald. She did experience some regrowth, but her hair remained severely thin, requiring use of a scalp prosthesis.

Before chemotherapy she had no history of hair loss. Her medical history was significant for treated

From the Dermatopathology Section, Department of Dermatology, Boston University School of Medicine,[a] and Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine.[b]
Funding sources: None.
Conflicts of interest: None declared.
Reprint requests: Ben Tallon, MBChB, Skin Pathology Laboratory, Boston University School of Medicine, 609 Albany St, Boston, MA 02118-2515. E-mail: bentallon@gmail.com.
Published online ■■■
0190-9622/$36.00

doi:10.1016/j.jaad.2009.06.063

hypothyroidism, and she had a family history of androgenetic alopecia in her father. Her scalp was otherwise asymptomatic and she had received no treatment.

Physical examination revealed severe diffuse hair loss most prominent over the crown (Fig 1). There was no inflammation or evidence of scarring. A single eyebrow was noted, which the patient stated appeared recently. Her nails appeared normal.

A 4-mm punch biopsy specimen was taken from the right frontal scalp, fixed in 10% neutral buffered formaldehyde, bisected horizontally, serially sectioned, and stained with hematoxylin and eosin. The dominant finding was a marked reduction in anagen hair follicles and the presence of multiple linear aggregates of basaloid epithelium, likely representing remnants of her hair follicles (Fig 2). These structures appeared similar to telogen hair follicles, though they were more slender and branched, and did not produce a hair shaft. Counting these as hair follicles, the total number of follicular units (12) was normal (0.9 per square millimeter), although there were only two remaining unaffected terminal anagen hair follicles. There was no significant perifollicular inflammation, and only mild perifollicular fibrosis. Sebaceous glands were preserved.

Because follicular structures were not completely absent, a trial of topical 2% minoxidil, administered twice daily, was initiated.

CAPSULE SUMMARY

- Chemotherapy-induced hair loss is typically considered completely reversible, but this is not always the case.
- This paper describes a patient remarkable for permanent hair loss following chemotherapy for breast cancer in the absence of bone marrow transplantation, the usual setting for permanent chemotherapy-induced alopecia.
- The literature on permanent chemotherapy is reviewed, and new histologic findings are described.
- Physicians and patients need to be aware of the rare possibility that alopecia following chemotherapy can be persistent.

DISCUSSION

Chemotherapy-induced alopecia (CIA) is typically reversible. Many chemotherapeutic agents have the ability to cause alopecia, the severity of which depends on the route of administration as well as the dose and frequency of administration.[1] Cytotoxic effects on hair follicles results in temporary hair loss until the telogen phase is complete and a new hair cycle begins, typically within 3 to 6 months.

Two of the 3 agents used in our patient's chemotherapy regimen, docetaxel and carboplatin, are well known to cause reversible alopecia. The World Health Organization criteria for chemotherapy-induced alopecia is grade 0 = no loss, grade 1 = mild hair loss, and grade 2 = pronounced or complete hair loss. Docetaxel, a taxane anticancer drug extracted from the European yew, exerts its cytotoxic effect by promoting and stabilizing microtubule assembly. In phase II trials of docetaxel at a dose of 100 mg/m^2, the incidence of alopecia was 83.4%, with all hair loss categorized as grade 1 or 2.[10] The DNA alkylating agent carboplatin, at a dose of 250 to 400 mg/m^2, causes mild alopecia in only 5% of cases.[11] Trastuzumab is a monoclonal antibody against HER2, a tyrosine kinase that is part of the human epidermal growth factor receptor family. It lacks the common side effects of neutropenia, mucositis and alopecia, and does not appear to increase the rate of hair loss when combined with standard chemotherapy for metastatic breast cancer.[12,13] The combination of docetaxel, 70 mg/m^2, and carboplatin AUC 5 has been reported to result in 26 of 26 patients experiencing grade 1 or 2 alopecia.[14]

Permanent CIA, defined as an absence of or incomplete hair regrowth 6 months beyond completion of chemotherapy,[1] is rare. It was first described in 1991 in 6 patients following chemotherapy conditioning for bone marrow transplantation.[7] All but one of the subsequent reports[2-6,8] have been in patients receiving BMT, usually for hematologic malignancies. One series of patients had permanent alopecia following BMT for advanced breast cancer.[4]

Two patients, in whom severe, irreversible alopecia developed following standard-dose docetaxel and paclitaxel for local recurrence of breast cancer, were recently reported.[9] The clinical findings were similar to those of our case with diffuse, marked thinning of scalp hair and, in one patient, generalized over the body without signs of scarring.

Permanent CIA has been described following the use of busulphan, cyclophosphamide, thiotepa, melphalan, etoposide, carboplatin, docetaxel, and paclitaxel.[2-9] Its reported incidence varies widely, ranging from 0.9% to 43%.[2,7] Busulphan is the most commonly implicated agent. The data regarding the relationship between chemotherapy dose and persistent alopecia are conflicting. Increased quantitative exposure to carboplatin and thiotepa[4] and

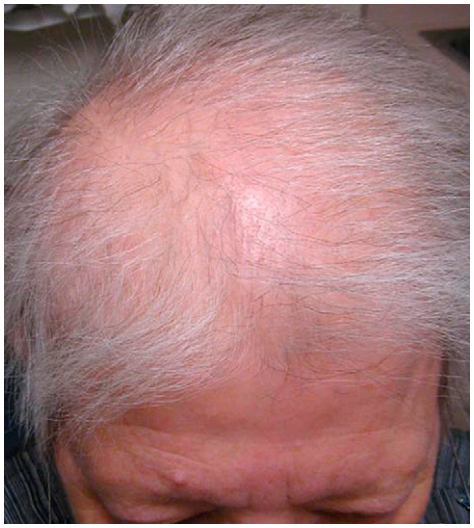

Fig 1. Diffuse thinning of hair on the scalp without inflammation or scarring.

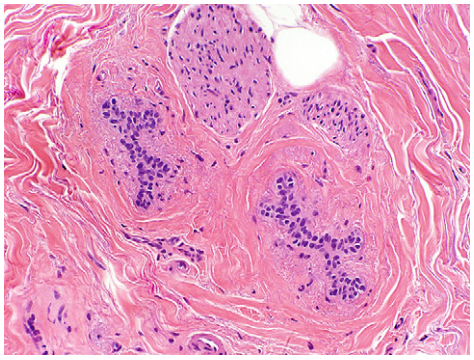

Fig 2. Punch biopsy specimen from right frontal scalp revealing linear aggregates of basaloid epithelium with only mild perifollicular fibrosis. (Hematoxylin-eosin stain, original magnification ×20.)

higher busulphan[6] concentrations have been linked to an increased risk, whereas no dose response was seen with cyclophosphamide.[4] Permanent alopecia has also been described in low-dose regimens, causing reduced peak plasma levels.[4] While AUC exposure, cumulative dose, and combined chemotherapeutic agent effects are important variables,[8] individual variation in the bioavailability of chemotherapeutics is seen[15] and may influence the occurrence of toxicity.

Description of the histopathology of permanent alopecia following chemotherapy is limited to 4 of the published reports.[3,5,7,9] In all cases there was a severe reduction in the total number of hairs, as in our patient, and no inflammation or fibrosis was present. One of the two recent cases[9] showed an increased number of vellus hairs, whereas the other had a peribulbar lymphocytic infiltrate. The unique finding in our patient was that of thin epithelial structures thought to represent remnants of the secondary hair germ of late-stage telogen follicles. Their significance is uncertain, but it appears that these structures may be insufficient to induce formation of a new hair bulb to generate a new hair shaft. Why these changes were not noted in the previous reports is unclear. There do appear to be similar structures seen in a photomicrograph in the report by Baker et al.[7] Perhaps these residual follicular epithelial aggregates were present but not obvious, or maybe they are transient and had already undergone complete involution.

Why some patients develop permanent, rather than temporary, alopecia following chemotherapy is unknown. Chemotherapy targets replicating cells within the hair matrix, resulting in rapid shedding of anagen hairs,[16] and also appear to be capable of inducing a shift into telogen.[17] High-dose or repeated chemotherapy is thought to delay hair regrowth because of a telogen effluvium accompanying the usual anagen effluvium.[5] It is postulated that permanent damage to the hair follicle may result from direct toxicity of high-dose chemotherapy on stem cells or hair matrix cells, or separation of the matrix cells from the dermal papilla.[5] Alternatively, maybe the chemotherapy affects the signaling to the secondary hair germ,[18,19] resulting in the appearance of poorly developed telogen germinal units seen on histology.

This is the second report of permanent alopecia in a patient who received adjuvant chemotherapy for breast cancer and not a conditioning regimen prior to BMT. The lack of evidence for alopecia with trastuzumab, and the exposure to only a single infusion of standard dose carboplatin, suggests that docetaxel is the implicated agent. The morbidity of chemotherapy-associated hair loss should not be underestimated, particularly given the increasing reports of permanent alopecia. This case demonstrates the risk of permanent hair loss following adjuvant chemotherapy for breast cancer. The histologic finding of replacement of anagen hair follicles by linear columns of basaloid epithelium has not been previously reported, to our knowledge, and likely portends a poor prognosis for regrowth. Whether this finding is due to toxic damage to stem cells or specific interference with active signaling pathways in susceptible individuals is unknown and requires further research.

REFERENCES

1. Dorr VJ. A practitioner's guide to cancer-related alopecia. Semin Oncol 1998;25:562-70.

2. Machado M, Moreb JS, Khan SA. Six cases of permanent alopecia after various conditioning regimens commonly used in hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;40:979-82.
3. Tosti A, Piraccini BM, Vincenzi C, Misciali C. Permanent alopecia after busulfan chemotherapy. Br J Dermatol 2005; 152:1056-8.
4. de Jonge ME, Mathôt RA, Dalesio O, Huitema AD, Rodenhuis S, Beijnen JH. Relationship between irreversible alopecia and exposure to cyclophosphamide, thiotepa and carboplatin (CTC) in high-dose chemotherapy. Bone Marrow Transplant 2002;30:593-7.
5. Tran D, Sinclair RD, Schwarer AP, Chow CW. Permanent alopecia following chemotherapy and bone marrow transplantation. Australas J Dermatol 2000;41:106-8.
6. Ljungman P, Hassan M, Békássy AN, Ringdén O, Oberg G. Busulfan concentration in relation to permanent alopecia in recipients of bone marrow transplants. Bone Marrow Transplant 1995;15:869-71.
7. Baker BW, Wilson CL, Davis AL, Spearing RL, Hart DN, Heaton DC, et al. Busulphan/cyclophosphamide conditioning for bone marrow transplantation may lead to failure of hair re-growth. Bone Marrow Transplant 1991;7:43-7.
8. Vowels M, Chan LL, Giri N, Russell S, Lam-Po-Tang R. Factors affecting hair regrowth after bone marrow transplantation. Bone Marrow Transplant 1993;12:347-50.
9. Prevezas C, Matard B, Pinquier L, Reygagne P. Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. Br J Dermatol 2009;160:883-5.
10. Cortes JE, Pazdur R. Docetaxel. J Clin Oncol 1995;13:2643-55.
11. Thatcher N, Lind M. Carboplatin in small cell lung cancer. Semin Oncol 1990;17(1 Suppl. 2):40-8.
12. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
13. Baselga J. Clinical trials of single-agent trastuzumab (Herceptin). Semin Oncol 2000;27(5 Suppl. 9):20-6.
14. Aoki Y, Sato T, Tsuneki I, Watanabe M, Kase H, Fujita K, et al. Docetaxel in combination with carboplatin for chemo-naive patients with epithelial ovarian cancer. Int J Gynecol Cancer 2002;12:704-9.
15. Hassan M, Ljungman P, Bulme P, et al. Busulphan bioavailability. Blood 1994;84:2144-50.
16. Sinclair R. Diffuse hair loss: Anagen effluvium. In: Sinclair R, Banfield C, Dawber R, editors. Handbook of diseases of the hair and scalp. Oxford: Blackwell Science; 1999. pp. 70-4.
17. Bleiker TO, Nicolaou N, Traulsen J, Hutchinson PE. 'Atrophic telogen effluvium' from cytotoxic drugs and a randomized controlled trial to investigate the possible protective effect of pretreatment with a topical vitamin D analogue in humans. Br J Dermatol 2005;153:103-12.
18. Bayer-Garner IB, Sanderson RD, Smoller BR. Syndecan-1 is strongly expressed in the anagen hair follicle outer root sheath and in the dermal papilla but expression diminishes with involution of the hair follicle. Am J Dermatopathol 2002;24:484-9.
19. Peters EM, Stieglitz MG, Liezman C, Overall RW, Nakamura M, Hagen E, et al. P75 neurotrophin receptor-mediated signaling promotes human hair follicle regression (catagen). Am J Pathol 2006;168:221-34.