Case Report

Gefitinib-associated vitiligo: report in a man with parotid squamous cell carcinoma and review of drug-induced hypopigmentation

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Abstract

Gefitinib is a tyrosine kinase inhibitor that targets and inhibits epidermal growth factor receptors. It was initially used to treat non-small cell lung cancer but has increasingly been used for other solid tumors such as those in the breast, colorectal sites, and head and neck, as in our patient. Vitiligo is an autoimmune disorder that results in the destruction of melanocytes and subsequent skin depigmentation and hypopigmentation. Previously described mucocutanous side effects of gefitinib at 250-500 mg/day include alopecia, asteatotic dermatitis, desquamation, hyperpigmentation, papulopustular acneiform eruption, pruritus, seborrheic dermatitis, and skin fragility. A 54-year-old man with metastatic squamous cell carcinoma to the parotid gland developed vitiligo within 1 month of starting gefitinib therapy. We retrospectively reviewed the medical literature using PubMed, searching: (1) gefitinib side effects, (2) drugs and (3) vitiligo. The patient with gefitinib-induced vitiligo continued to receive treatment with the drug during which time areas of skin hypopigmentation persisted and progressed. Etiology of drug-induced vitiligo includes alopecia areata therapies, anticonvulsants, antimalarials, antineoplastics, anti-Parkinson medications, and other miscellaneous drugs. No other individuals have been described with gefitinib-induced vitiligo. Albeit rare, gefitinib may be associated with the development of vitiligo.

Keywords: cancer, drug, EGFR inhibitors, gefitinib, hypopigmentation, vitiligo

Introduction

Gefitinib is an epidermal growth factor receptor (EGFR) inhibitor initially approved for non-small cell lung cancers but has increasingly been used for the treatment of breast cancer and other solid tumors [1]. Vitiligo is an autoimmune condition associated with acquired hypopigmentation of the skin. We describe a man with squamous cell carcinoma metastatic to the parotid gland who developed diffuse hypopigmentation while successfully being treated with gefitinib for his metastatic neoplasm.
Figure 1 (a and b). Distal view of the chest (a) and closer view of the left anterolateral neck (b) showing areas of gefitinib-induced vitiligo. Hypopigmentation of this area was more marked on the left side, which received radiation treatment for metastatic squamous cell carcinoma to his left parotid.

Case report

A 54-year-old man presented with a left parotid mass and a history of non-melanoma skin cancers. Biopsy of the tumor in 6/2007 revealed metastatic squamous cell carcinoma with a presumptive cutaneous primary. The patient started induction antineoplastic therapy in 7/2007; he received 250 mg gefitinib daily. After 2 weeks, the daily dose was increased to a maintenance dose of 500 mg.

The patient underwent parotidectomy and selective neck dissection in 9/2007. He subsequently developed recurrent squamous cell carcinoma to the left parotid and the left cutaneous neck; he received a total dose of 60 Gy of radiation therapy from 11/2007 to 12/2007. Gefitinib treatment was withheld during his radiotherapy and was reinitiated in 1/2008 until 1/2009.

The patient noticed lightening of his skin within 3 to 4 weeks after starting gefitinib. In 9/2008, after 14 months of gefitinib treatment, the patient’s physicians described an extensive and progressive loss of skin pigmentation on the arms, upper back, neck, face, left buttock, and right chest. Two months later (11/2008), he was seen by a dermatologist (PRC) who confirmed the development of hypopigmented areas of the patient’s skin.

Laboratory studies demonstrated normal hemoglobin, hematocrit, thyroid stimulating hormone, and thyroxine. Hence, vitiligo associated with either pernicious anemia or thyroid disease was excluded. In addition, there was no personal or family history of thyroid disease or pernicious anemia.

The patient’s metastatic squamous cell carcinoma had an excellent response to the gefitinib. The drug was continued in spite of the progression of hypopigmented skin areas. In 1/2009 he was considered to be free of the metastatic tumor and gefitinib therapy was discontinued.

The patient returned for another dermatology evaluation in 9/2012. Complete cutaneous examination showed persistence of his gefitinib-induced vitiligo that had originated after the initiation of his antitumor therapy (Figures 1-3).
Figure 2 (a and b). Distant (a) and closer (b) views of the back of a 54-year-old man with gefitinib-induced vitiligo show large patches of either decreased or absent pigment. Allergic contact dermatitis to adhesive (b) is also noted on the right scapula.

Figure 3 (a and b). Closer views of the anterior (a) and posterior (b) distal legs show symmetrically distributed areas of gefitinib-associated vitiligo in a 54-year-old man with metastatic squamous cell carcinoma to the parotid gland.

Discussion

EGFR comprises a family of receptors that include human epidermal factor (HER1) [1]. EGFR-HER1 is a transmembrane glycoprotein of the tyrosine kinase growth factor family that is expressed in human tissue. This protein is regulated to control cell growth and proliferation [1].

Gefitinib is an orally active reversible tyrosine kinase inhibitor that targets the EGFR. It does so by blocking the intracellular ATP-binding site thereby not only preventing phosphorylation but also inhibiting growth and proliferation factors [1,2]. Gefitinib is currently used to treat a wide variety of malignant solid tumors that overexpress EGFR such as carcinomas of the breast, colon, lung, and rectum. More recently the drug has been used to treat head and neck tumors [1]. In our patient, the drug was used as monotherapy for metastatic squamous cell carcinoma to the parotid gland and achieved an excellent clinical response.
Several mucocutaneous side effects have been described in patients using EGFR inhibitors. Similar to other EGFR inhibitors, gefitinib has been associated with alopecia, asteatotic dermatitis, desquamation, hyperpigmentation, papulopustular acneiform eruption, pruritus, seborrheic dermatitis, skin fragility, and trichomegaly [2-7]. Gefitinib-induced hypopigmentation has not previously been observed. However, drug-associated vitiligo has recently been reported with the use of another tyrosine kinase inhibitor, dasatinib [8]. A young man was treated with dasatinib for acute lymphoid leukemia and developed depigmentation of areas on his neck, hands, hair, eyelashes, and eyebrows. The authors speculate that the depigmentation is associated with mutations of the proto-oncogene c-Kit, a gene that encodes a class III tyrosine kinase receptor, specifically deletion of the Steel and Dominant White spotting loci. In addition, blockade of the stem cell factor ligand of the c-Kit signal transduction pathway, which is involved in the survival of melanocytes during migration and proliferation in the anagen hair follicles, is also postulated to be involved in the drug-induced hypopigmentation [9-11]. It is intriguing to postulate that vitiligo associated with gefitinib-another tyrosine kinase inhibitor-may be secondary to a similar mechanism of pathogenesis.

Vitiligo results from autoimmune-mediated destruction of melanocytes and clinically manifests as partial and/or total loss of skin pigment. It is traditionally based on the morphologic presentation of the absence of cutaneous pigment; it typically presents as amelanotic macules and patches that are symmetrically distributed. Affected areas often include distal digits and periorificial sites. Several hypotheses have been proposed to explain the pathogenesis of vitiligo; some of them include genetic factors, neurologic factors, toxic metabolites, and lack of melanocyte growth factors [12]. Albeit rare, drug-induced vitiligo has been observed (Table 1) [13-43].

Patients with antineoplastic agent-induced vitiligo have been described (Table 2) [16-23,25,39-43]. Neither a specific class of antineoplastic drugs nor a unique tumor origin or histology has been associated with the development of cutaneous hypopigmentation. Similarly, antitumor drug-associated vitiligo has not been linked to a specific route of administration; cancer therapy-related hypopigmentation has occurred following not only intravenous administration of the agent, but also oral, subcutaneous, and topical delivery of the drug.

The onset of drug-induced vitiligo has been found to occur as early as a couple of days to as long as 6 months after the associated medication has been started. Because many of the patients with drug-induced vitiligo respond to antineoplastic therapy, their drug treatment is continued and even subsequently increased in dosage in spite of the progressive skin hypopigmentation that may occur. Additionally, vitiligo has persisted in many of these individuals even after discontinuation of the associated drug.

**Conclusion**

EGFR inhibitors, such as gefitinib, are associated with several mucocutaneous side effects. The observation of antineoplastic therapy-induced vitiligo in a patient with metastatic cancer is uncommon. Our patient is unique; he developed extensive skin hypopigmentation beginning within 1 month after initiating treatment with gefitinib for metastatic squamous cell cancer to his parotid gland. Subsequently, his loss of cutaneous pigment progressed while he continued to receive gefitinib therapy and persisted even 3 years after discontinuing the agent.

Drug-induced vitiligo has also been associated with antineoplastic agents including doxorubicin, imatinib, imiquimod, interferon alpha, interferon beta, interleukin-2, interleukin-4, mitoxantrone, and survivin inhibitor. It does not appear to be related to a specific cancer type, tumor histology, route of administration, or duration of drug therapy. The development of chemotherapy-associated vitiligo is not a drug-limiting side effect in patients whose cancer is responding to the agent. The subsequent hypopigmentation tends to persist after discontinuing treatment with the vitiligo-inducing drug.

Recently vitiligo associated with dasatinib, another tyrosine kinase inhibitor similar to gefitinib, has been described in a leukemic pediatric patient. The proto-oncogene c-Kit mutations and blockade of the stem cell factor ligand and c-Kit signal transduction pathway of melanocytes has been postulated to be involved in the pathogenesis of the drug-induced hypopigmentation [9-11]. In conclusion, albeit rare, tyrosine kinase inhibitors such as gefitinib and dasatinib may be associated with the development of vitiligo.

**Table 1. Drugs associated with vitiligo development**

<table>
<thead>
<tr>
<th>Medication class and drug</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine [a]</td>
<td>20</td>
</tr>
<tr>
<td>Clonazepam [a]</td>
<td>20</td>
</tr>
<tr>
<td>Phenytoin [a]</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 2. Antineoplastic agent-induced vitiligo [a]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rou</th>
<th>Dose Frequency</th>
<th>Cancer/Disease</th>
<th>Vitiligo Location</th>
<th>Onset [b]</th>
<th>RTT/P</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasa</td>
<td>PO</td>
<td>100 Mg BID</td>
<td>ALL</td>
<td>N,Ha,Hai,EL,EB</td>
<td>1 Mo</td>
<td>NS</td>
<td>8</td>
</tr>
<tr>
<td>Dox [c]</td>
<td>PO</td>
<td>4 Cy Q 2 Wks</td>
<td>BC</td>
<td>Lblá[d]</td>
<td>2 Mo</td>
<td>P</td>
<td>12-14</td>
</tr>
<tr>
<td>Gef</td>
<td>PO</td>
<td>500Mg QD for 12Mo</td>
<td>SCCP</td>
<td>Gen</td>
<td>1Mo</td>
<td>P</td>
<td>CR</td>
</tr>
<tr>
<td>Il2[e]</td>
<td>IV</td>
<td>HD1, 600,000 U/Kg/dose IV Q 8 H, Ma 14 doses 5 D</td>
<td>MM</td>
<td>F, N, Ch, UE</td>
<td>1 Mo</td>
<td>NS</td>
<td>37</td>
</tr>
<tr>
<td>Il4</td>
<td>IV</td>
<td>600 µg/M² Q8H for 2 x 14 D Cy</td>
<td>MM</td>
<td>B, Ch F, LE</td>
<td>1 Mo</td>
<td>P</td>
<td>38</td>
</tr>
<tr>
<td>Im[f]</td>
<td>PO</td>
<td>400 Mg QD</td>
<td>CML</td>
<td>90% BSA</td>
<td>NS</td>
<td>P=12Mo</td>
<td>19</td>
</tr>
<tr>
<td>Im[g]</td>
<td>PO</td>
<td>400-600 Mg QD</td>
<td>CML</td>
<td>Pe, Ha</td>
<td>6Mo</td>
<td>NS</td>
<td>39</td>
</tr>
</tbody>
</table>

[a] These drugs are included in an abstract, which presented a meta-analysis of reported cases of vitiligo-induced by drug. However, we could not identify the original report for the drug in our search of the PubMed database.

[b] In a retrospective study of 421 patients who underwent allogenic hemataopoietic cell transplant, 6 individuals with chronic myeloid leukemia subsequently developed vitiligo; 5 of those patients developed severe graft-versus-host-disease. All but one patient was conditioned for allogenic hemataopoietic cell transplant by busulphan and cyclophosphamide. Therapy with methotrexate and cyclosporine A for as short as 3 months to as long as 12 months was also given for graft-versus-host-disease prophylaxis. One patient received conditioning with fludarabine and busulphan and prophylaxis against graft-versus-host-disease with mycophenolate mofetil for 1 year after transplantation. Additional patients with transplant-induced vitiligo have also been described [18].
| If2a [h] | SQ | 180 µg/Wk for 12 Wk | HCV | Inj, BLUA | 4 Mo | P | 15 |
| If2a [i] | SQ | 180 µg/wk for 24 Wk | HCV | Inj, Gen | 5 Mo | P; > Gen | 15 |
| If2b | SQ | 3 MU 3X/Wk for 16 Wk | HBV | Gen | 6 Mo | BD=F | P= >12m; LFU | 35 |
| If2b | SQ | 3 MU 3X/Wk for 12 Wk | HCV | Gen | 3 Mo | P | 36 |
| Imiq [j] | Top | 5% Cr 5/Wk for 13 Wk | BCC | Rt FA | 3.25 Mo | BD | 0.05%, P= 18 Mo | 16 |
| Mito [k] | SQ | NS | BC | A, F, L,N | NS | P=Capa tx 15 yr | 12, 21 |
| Surl | IV | 4.8 Mg/M²/D C Inf for 168 H | MM | A, Ha | <1 Mo | P= > 2Yr | 17 |
| Vem [l] | PO | 960 Mg BID | MM | F, N | 0.5 Mo | NS | 46 |

[a] Abbreviations: A=arm; ALL=Acute Lymphoid Leukemia; B=back; BC= metastatic breast cancer; BCC=basal cell carcinoma; BD= Betamethasone dipropionate; BID=twice a day; BLUA=Bilateral upper arms; BSA=body surface area; C=continuous; Capa=capacetabine; Ch=chest; CML= chronic myeloid leukemia; Cr=cream; CR=case report; Cy=cycle; Cyc=cyclophosphamide; D=days; Dox=doxorubicin; Dz= disease; EL=eyelash; EB=eyebrows; F=face; Fa=failed; FA=forearm; H=hour; Ha=hands; Hai=hair; HBV= hepatitis B; HCV= hepatitis C; chronic; HDI=high dose; If2alpha=interferon-2alpha; If2b=interferon-2alpha; Il=Interleukin; Im=imatinib mesilate; Imiq=imiquimod; Inf=infusion; Inj= injection site; IV=intravenous Gef= Gefitinib; Kg=kilogram; Gen=generalized; Lbla= Left Breast and Left Axilla; Le=left; LE=lower extremity; LFU=lost to follow up; Ma=maximum; M²= meters squared; µg=microgram; Mg=milligram; Mito= mitoxantrone; MM=malignant melanoma (stage IV); Mo=months; MU= million units; N=neck; NS= not stated; P=persistence; Pe=penis; PO=oral; Q=every; QD=daily; Rt=right; Ref=reference; Rou=route; RTT=Response to therapy directed toward vitiligo, including discontinuation of drug; SCCP=squamous cell carcinoma metastatic to parotid gland; SQ=subcutaneous injection; Surl= survivin Inhibitor; Top=topical; Tx=treatment; U=units; UE=upper extremity; Vem=Vemurafenib; Wk=weeks; Yr=years, - = other

[b] The duration of time between starting the drug and the onset of vitiligo.

[c] Both doxorubicin and cyclophosphamide were used as therapy when vitiligo developed. Since cyclophosphamide has been used as a treatment for vitiligo [13-14], it is more likely that doxorubicin is the associated drug causing the development of vitiligo. Interestingly, the patient also had a history of intermittent vitiligo that was not evident on skin examination at the time of diagnosis of her breast cancer.

[d] Skin overlying left breast mass and axilla.

[e] The patient was previously on temozolomide (75 mg/m²/day orally on a 21 out of 28 day schedule). The investigators postulate that the onset of vitiligo-like depigmentation in this individual was Il2-mediated secondary to the (1) short interval between the discontinuation from the temozolomide regimen and the onset of vitiligo, (2) the patient’s original objective response to the temozolomide-Il2 based therapy, and (3) the lack of any association between vitiligo and temozolomide therapy in melanoma.

[f] The patient had pre-existing generalized vitiligo. The percentage of body surface area involved was 36% before treatment and 90% after treatment with imatinib mesilate.

[g] This is the initial observation of imatinib-induced vitiligo [39]. Additional patients with imatinib-induced vitiligo have subsequently been reported [40].

[h] The patient was concurrently taking ribavirin 1,000mg daily as part of the treatment regimen.

[i] The patient was concurrently taking ribavirin 800 mg daily as part of the treatment regimen.

[j] Additional patients with imiquimod-induced vitiligo have also been reported [16,41-45].

[k] The paper reports that mitoxantrone, not capacetabine, induced the development of vitiligo. Capacetabine was used for the treatment of her vitiligo.

[l] Additional similar case has been reported in the same reference.

References


