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CASE REPORT

Vorasidenib-Induced Trichomegaly and Hypertrichosis: a New Side Effect in a Patient with Diffuse Astrocytoma

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ABSTRACT

Vorasidenib, an oral dual inhibitor targeting mutant enzymes isocitrate dehydrogenase 1 and 2, is utilized in the management of diffuse low-grade gliomas. Despite limited documentation of its adverse events, we present the case of a 44-year-old male who exhibited trichomegaly and hypertrichosis of body hair, eyebrows, and eyelashes following one month of vorasidenib treatment. Notably, the patient experienced diffuse hair regrowth on the scalp, including in areas affected by severe androgenetic alopecia. This report holds significance as it highlights a previously unreported side effect, thereby enhancing our understanding of emerging therapies for brain tumors and their associated adverse reactions.

Keywords: Vorasidenib; Trichomegaly; Hypertrichosis; Oncology therapy; Astrocytoma; Side effect

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Key Summary Points
Why carry out this study?
Vorasidenib, an oral dual inhibitor targeting mutant enzymes isocitrate dehydrogenase 1 and 2 (IDH1/2), emerged as a new therapeutic option for low-grade diffuse gliomas resistant to conventional treatments, but dermatological side effects were not well documented
What did the study ask?
This study examined dermatological side effects, specifically trichomegaly and hypertrichosis, in a patient treated with vorasidenib for a diffuse astrocytoma
What was learned from the study?
Vorasidenib treatment was associated with the development of trichomegaly and hypertrichosis, phenomena never before reported in connection with IDH1/2 inhibitors
Careful monitoring of side effects in new treatments for brain tumors is crucial to optimize treatment strategies and improve patient care

INTRODUCTION

Vorasidenib, an oral dual inhibitor targeting mutant enzymes isocitrate dehydrogenase 1 and 2 (IDH1/2), represents a significant advancement in the treatment of brain tumors, particularly diffuse low-grade gliomas resistant to conventional approaches, such as surgery and radiotherapy [1]. Its ability to cross the blood–brain barrier is noteworthy, as it enables direct action within the central nervous system. This emergence in the treatment landscape offers hope for patients facing challenging prognoses. Inhibitors of mutant IDH1 and IDH2 have already shown efficacy in other cancers, such as acute myeloid leukemia and cholangiocarcinoma. However, the introduction of vorasidenib brings forth a new dimension in the treatment of brain tumors, addressing a pressing need for effective therapies in this realm. The reported adverse events associated with vorasidenib include increased transaminases, fatigue, headache, diarrhea, nausea, dizziness, epileptic seizures, insomnia, tinnitus, anemia, abdominal pain, dyspepsia, constipation, and electrolyte alterations [1, 2].

CASE PRESENTATION

The case study presented involves a 44-year-old male diagnosed with diffuse astrocytoma, grade G2, IDH-mutant, without 1p36/19q16, and methylated MGMT. Following a left frontotemporal craniotomy in 2019, the patient was enrolled in the INDIGO protocol (trial no. NCT04164901). He also started taking levetiracetam at 250 mg/day for resulting epilepsy. After a placebo administration, in July 2023, vorasidenib treatment commenced at a dosage of 40 mg/day. After 4 weeks, the patient developed trichomegaly and hypertrichosis characterized by increased length and thickness of body hair and eyebrows and eyelashes. Hair regrowth started diffusely on the scalp and also in androgen-sensitive area where the patient is affected by severe androgenetic alopecia (Fig. 1). Despite the dermatological side effects, vorasidenib was continued for its beneficial effect on the underlying disease.

DISCUSSION

In IDH inhibitor clinical trials, the cutaneous adverse events (CAEs) frequently observed include edema, rash, and pruritus. Edema has been documented in 32% of cases, while rash of any severity ranges from 18 to 26%, and pruritus affects 9–14% of patients on IDH inhibitors [3]. To the best of our knowledge, no precedent report of hypertrichosis or trichomegaly has ever been related to the use of vorasidenib or any other IDH inhibitor.

IDH enzymes normally catalyze the decarboxylation of isocitrate to generate α-ketoglutarate (αKG), but recurrent mutations at Arg(132) of IDH1 and Arg(172) of IDH2 confer a neomorphic

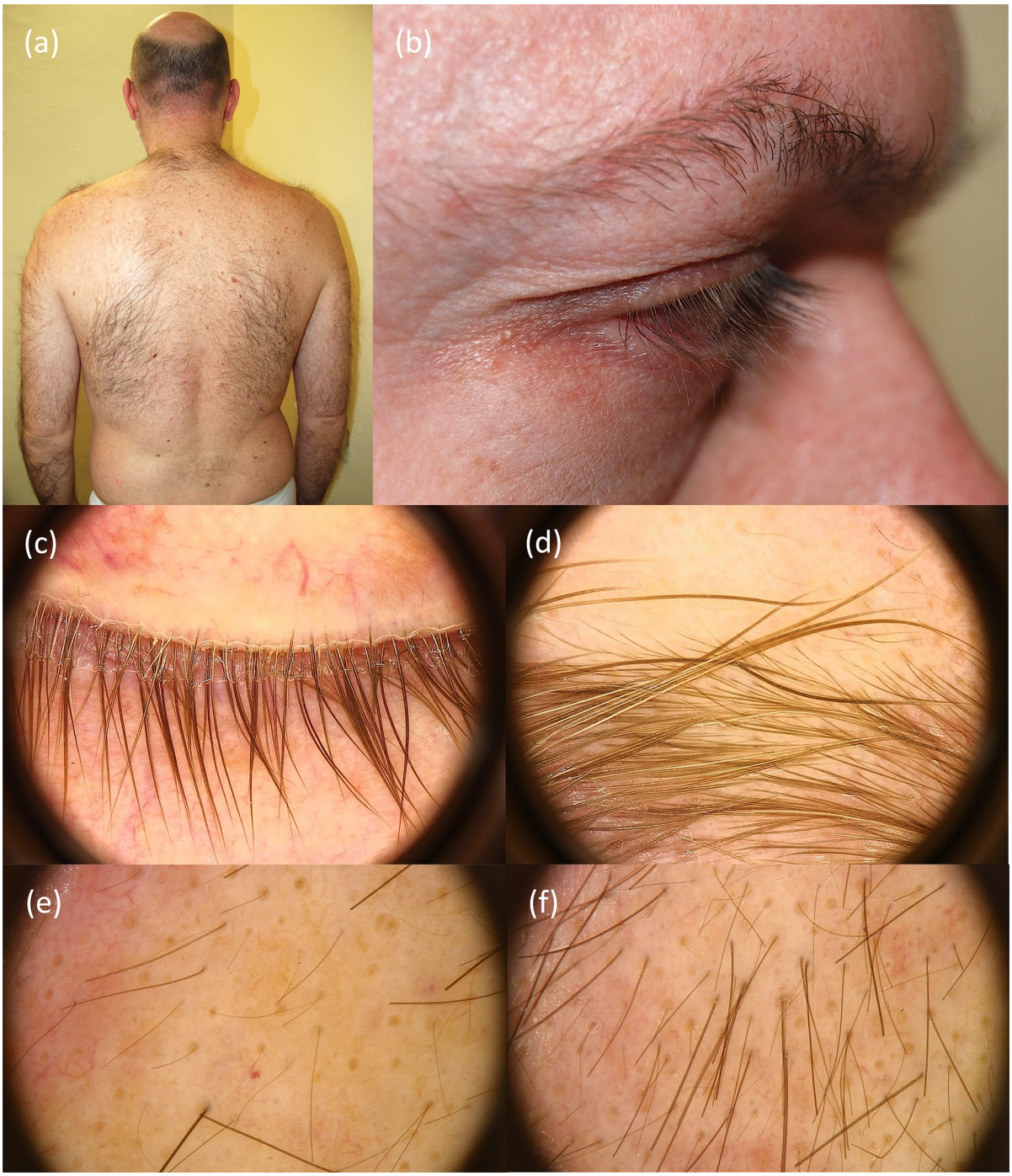

Fig. 1 Hypertrichosis affecting both body hair (**a**) and eyebrows (**b**), accompanied by trichomegaly (**b**). Through digital trichoscopy at 20 × magnification, distinct features, such as trichomegaly, defined by the elongation and thickening of the eyelashes (**c**), as well as increased eyebrow density and thickness (**d**), are discernible. Trichoscopy of the scalp showed a progressive increase in hair diameter at the first evaluation (**e**), and after 5 months (**f**)

enzyme activity that catalyzes the reduction of αKG into an oncometabolite known as D-2-hydroxyglutamate (D2HG) [4]. By suppressing mutated IDH, vorasidenib could alter cellular metabolism and accumulate α-KG. Elevated α-KG levels activate pathways for hair follicle regeneration and anagen hair growth. Additionally, α-KG-induced autophagy contributes to hair follicle remodeling and regeneration, potentially leading to hypertrichosis and trichomegaly [5]. It is essential to note that there is no known association between levetiracetam and hypertrichosis/trichomegaly, ruling out any potential confounding effects from the adjunct epilepsy medication.

CONCLUSIONS

This case underscores the importance of vigilant monitoring for unexpected side effects in novel therapies for brain tumors. By expanding our understanding of treatment-related adverse events, we can better optimize therapeutic strategies and enhance patient care. Further research into the mechanisms underlying these phenomena is warranted to elucidate their clinical implications fully.

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Declarations

Conflict of Interest. S.C., L.R., F.B., and B.M.P. have no relevant financial or nonfinancial interests to disclose. M.S. is an editorial board member of Dermatology and Therapy. M.S. was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. The patient in this manuscript has given written informed consent to publication of his case details.

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