www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Erlotinib Induced Vasculitis

Authors
Dr. Ansar Hussain Hakeem[1], Prof. Shiekh Aejaz Aziz[2], Prof. AR lone[3], Prof. Gull Mohd. Bhat[4], Dr. Burhan Wani[5], Dr. HK. Imran Hussain[6]
[1]MD, DM Scholar Medical Oncology SKIMS Srinagar
[2]MD, DM Medical Oncology SKIMS Srinagar
[3]MD. Medical Oncology SKIMS, Srinagar
[4]MD, DM Medical Oncology, SKIMS, Srinagar
[5]MD Medical Oncology SKIMS
[6]MD SKIMS
Corresponding Author
Dr Ansar Hussain Hakeem
MD, DM Scholar Medical Oncology, SKIMS Srinagar
Add: Nawabagh, baghwanpora, lal bazar, Srinagar, 190023
Email: *Ansarhakim22@gmail.com*

Abstract

Erlotinib is a tyrosine kinase inhibitor and is approved in lung cancer especially in adenocarcinoma of lung with mutated EGFR. It has got minimal side effects, the most common toxicity being rash. We present a case of life threatening vasculitis caused by the same agent. This is the first case of vasculitis caused by erlotinib in the literature.

CASE PRESENTATION

5o year old female, non smoker presented with 3 weeks history of progressively increased breathlessness and chest pain. Examination revealed signs of pleural effusion on right side of chest, rest of examination was non revealing. CECT was suggestive of right lung mass and massive effusion on right side of chest. CT guided biopsy of lung lesion was suggestive of adenocarcinoma lung. The EGFR of biopsy specimen was mutated. Patient was started on Erlotinib but her symptoms worsened after taking 150 mg per day erlotinib orally for one month and she needed drainage of pleural effusion by intercostal tube drainage. Meanwhile she also developed edema and bluish discolouration of her feet (Figure) and nasal tip. Patient was put on supportive treatment but finally succumbed to her illness.

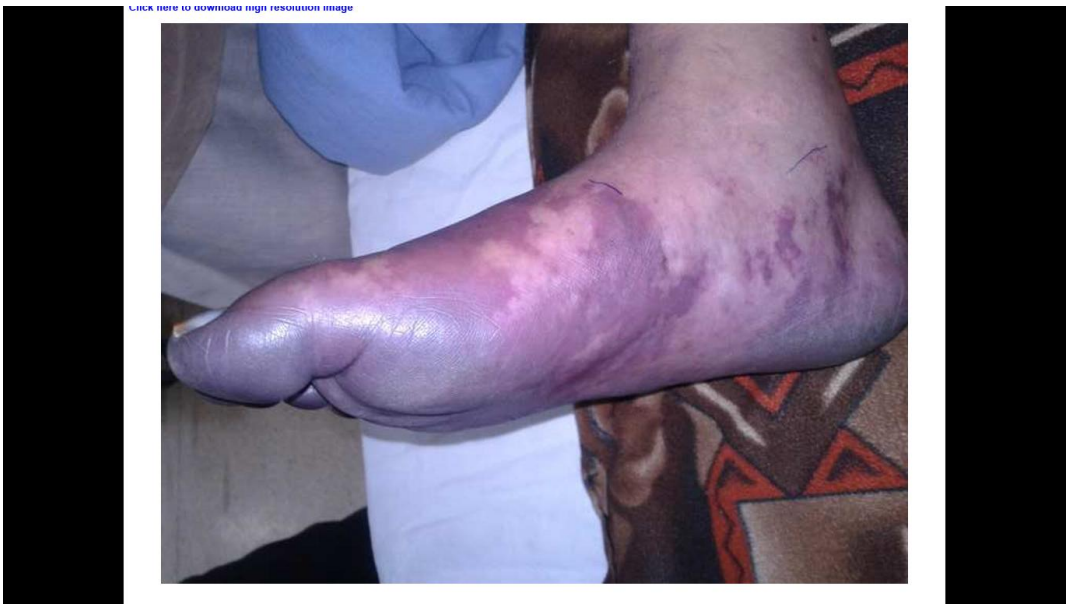

Figure Showing Vasculitis of Feet

DISCUSSION

The **epidermal growth factor receptor** (EGFR) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands.[1]The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer.[2]Epidermal growth factor and its receptor was discovered by Stanley Cohen of Vanderbilt University. Cohen shared the 1986 Nobel Prize in Medicine with Rita Levi-Montalcini for their discovery of growth factors

EGFR (epidermal growth factor receptor) exists on the cell surface and is activated by binding of its specific ligands, including epidermal growth factor and transforming growth factor α (TGFα) . ErbB2 has no known direct activating ligand, and may be in an activated state constitutively or become active upon heterodimerization with other family members such as EGFR. Upon activation by its growth factor ligands, EGFR undergoes a transition from an inactive monomeric form to an active homodimer[3] – although there is some evidence that preformed inactive dimers may also exist before ligand binding. In addition to forming homodimers after ligand binding, EGFR may pair with another member of the ErbB receptor family, such as ErbB2/Her2/neu, to create an activated heterodimer. There is also evidence to suggest that clusters of activated EGFRs form, although it remains unclear whether this clustering is important for activation itself or occurs subsequent to activation of individual dimers.

EGFR dimerization stimulates its intrinsic intracellular protein-tyrosine kinase activity. As a result, autophosphorylation of several tyrosine (Y) residues in the C-terminal domain of EGFR occurs.[4] This autophosphorylation elicits downstream activation and signaling by several other proteins that associate with the

phosphorylated tyrosines through their own phosphotyrosine-binding SH2 domains. These downstream signaling proteins initiate several signal transduction cascades, principally the MAPK, Akt and JNK pathways, leading to DNA synthesis and cell proliferation.[5] Such proteins modulate phenotypes such as cell migration, adhesion, and proliferation. Mutations that lead to EGFR overexpression (known as upregulation) or overactivity have been associated with a number of cancers, including lung cancer, anal cancers[6] and glioblastoma multiforme. These somatic mutations involving EGFR lead to its constant activation, which produces uncontrolled cell division.[7] In glioblastoma a more or less specific mutation of EGFR, called EGFRvIII is often observed.[8] Mutations, amplifications or misregulations of EGFR or family members are implicated in about 30% of all epithelial cancers. The identification of EGFR as an oncogene has led to the development of anticancer therapeutics directed against EGFR (called "EGFR inhibitors"), including gefitinib,[9]erlotinib, afatinib, and icotinib[10] for lung cancer, and cetuximab for colon cancer.New drugs such as gefitinib and erlotinib directly target the EGFR. Patients have been divided into EGFR-positive and EGFR-negative, based upon whether a tissue test shows a mutation. EGFR-positive patients have shown a 60% response rate, which exceeds the response rate for conventional chemotherapy.[11]**Erlotinib hydrochloride** is a drug used to treat non-small cell lung cancer (NSCLC), pancreatic cancer and several other types of cancer. It is a reversible tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). Erlotinib has shown a survival benefit in the treatment of lung cancer in phase III trials. The SATURN (Sequential Tarceva in Unresectable NSCLC) study found that erlotinib added to chemotherapy improved overall survival by 19%, and improved progression-free survival (PFS) by 29%, when compared to chemotherapy alone.[12][13]

The U.S. Food and Drug Administration (FDA) has approved erlotinib for the treatment of locally advanced or metastatic non-small cell lung cancer that has failed at least one prior chemotherapy regimen.

In November 2005, the FDA approved erlotinib in combination with gemcitabine for treatment of locally advanced, unresectable, or metastatic pancreatic cancer.[14]

In lung cancer, erlotinib has been shown to be effective in patients with or without EGFR mutations, but appears to be more effective in patients with EGFR mutations.[15][16] Overall survival, progression-free survival and one-year survival are similar to standard second-line therapy (docetaxel or pemetrexed). Overall response rate is about 50% better than standard second-line chemotherapy.[16] Patients who are non-smokers, and light former smokers, with adenocarcinoma or subtypes like BAC are more likely to have EGFR mutations, but mutations can occur in all types of patients.

Common side effects of erlotinib include

- Rash occurs in the majority of patients. This resembles acne and primarily involves the face and neck. It is self-

limited and resolves in the majority of cases, even with continued use. Interestingly, some clinical studies have indicated a correlation between the severity of the skin reactions and increased survival though this has not been quantitatively assessed.[17] The *Journal of Clinical Oncology* reported in 2004 that "cutaneous [skin] rash seems to be a surrogate marker of clinical benefit, but this finding should be confirmed in ongoing and future studies."[18] The newsletter *Lung Cancer Frontiers* reported in its October 2003 issue, "Patients with moderate to severe cutaneous reactions [rashes] have a far better survival, than those with only mild reactions and much better than those with no cutaneous manifestations of drug effects."[19]

- Diarrhea
- Loss of appetite
- Fatigue
- Rarely, interstitial pneumonitis, which is characterized by cough and increased dyspnea. This may be severe and must be considered among those patients whose breathing acutely worsens.
- Rarely, ingrown hairs, such as eyelashes
- It has also been suggested that erlotinib can cause hearing loss.
- Partial hair loss (by strands, not typically in clumps)

Rare side effects include

- gastrointestinal tract toxicity
  - serious or fatal gastrointestinal tract perforations
- skin toxicity
  - bullous, blistering, and exfoliative skin conditions (some fatal)
  - Stevens–Johnson syndrome/toxic epidermal necrolysis [20]
- ocular disorders
  - corneal lesions
- Pulmonary toxicity
  - interstitial pneumonitis
  - bronchiolitis obliterans with organizing pneumonia
  - pulmonary fibrosis
  - fatal asymmetric interstitial lung disease[21]
  - the side effect which we reported i.e. vasculitis is first time reported in the literature and can be life threatning as we have seen.

REFERENCES

1. Herbst RS (2004). "Review of epidermal growth factor receptor biology". Int. J. Radiat. Oncol. Biol. Phys. 59 (2 Suppl): 21–6. doi:10.1016/j.ijrobp.2003.11.041. PMID 15142631.
2. Zhang H, Berezov A, Wang Q, Zhang G, Drebin J, Murali R, Greene MI (August 2007). "ErbB receptors: from oncogenes to targeted cancer therapies". J. Clin. Invest. 117 (8): 2051–8. doi:10.1172/JCI32278. PMC 1934579. PMID 17671639.
3. Yosef Yarden and Joseph Schlessinger (1987). "Epidermal Growth-Factor Induces Rapid, Reversible Aggregation of the

Purified Epidermal Growth-Factor Receptor". Biochemistry 26 (5): 1443–1451. doi:10.1021/bi00379a035. PMID 3494473.

4. J, Parker P, Waterfield MD (1984). "Autophosphorylation sites on the epidermal growth factor receptor". Nature 311 (5985): 483–5. doi:10.1038/311483a0. PMID 6090945.
5. Oda K, Matsuoka Y, Funahashi A, Kitano H (2005). "A comprehensive pathway map of epidermal growth factor receptor signaling". Mol. Syst. Biol. 1 (1): 2005.0010. doi:10.1038/msb4100014. PMC 1681468. PMID 16729045.
6. Walker F, Abramowitz L, Benabderrahmane D, Duval X, Descatoire V, Hénin D, Lehy T, Aparicio T (November 2009). "Growth factor receptor expression in anal squamous lesions: modifications associated with oncogenic human papillomavirus and human immunodeficiency virus". Hum. Pathol. 40 (11): 1517–27. doi:10.1016/j.humpath.2009.05.010. PMID 19716155.
7. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (May 2004). "Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib". N. Engl. J. Med. 350 (21): 2129–39. doi:10.1056/NEJMoa040938. PMID 15118073.
8. Kuan CT, Wikstrand CJ, Bigner DD (June 2001). "EGF mutant receptor vIII as a molecular target in cancer therapy". Endocr. Relat. Cancer 8 (2): 83–96. doi:10.1677/erc.0.0080083. PMID 11397666.
9. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M' (June 2004). "EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy". Science 304 (5676): 1497–500. doi:10.1126/science.1099314. PMID 15118125.
10. Liang, Wenhua; Wu, Xuan; Fang, Wenfeng; Zhao, Yuanyuan; Yang, Yunpeng; Hu, Zhihuang; Xue, Cong; Zhang, Jing; Zhang, Jianwei; Ma, Yuxiang; Zhou, Ting; Yan, Yue; Hou, Xue; Qin, Tao; Dinglin, Xiaoxiao; Tian, Ying; Huang, Peiyu; Huang, Yan; Zhao, Hongyun; Zhang, Li; Ganti, Apar Kishor (12 February 2014). "Network Meta-Analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations". PLoS ONE 9 (2): e85245
11. Jackman DM, Miller VA, Cioffredi LA, Yeap BY, Jänne PA, Riely GJ, Ruiz MG, Giaccone G, Sequist LV, Johnson BE (August 2009). "Impact of epidermal

growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials". Clin. Cancer Res. 15 (16): 5267–73. doi:10.1158/1078-0432.CCR-09-0888. PMC 3219530. PMID 19671843

12. 2009 - SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC.
13. April 2010 - Tarceva Indication Announcement Letter
14. Takimoto CH, Calvo E. "Principles of Oncologic Pharmacotherapy" in Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ (Eds) Cancer Management: A Multidisciplinary Approach. 11 ed. 2008.
15. Kobayashi, K.; Hagiwara, K. (2013). "Epidermal growth factor receptor (EGFR) mutation and personalized therapy in advanced nonsmall cell lung cancer (NSCLC)". Targeted Oncology 8 (1): 27–33. doi:10.1007/s11523-013-0258-9. PMC 3591525. PMID 23361373. edit
16. Qi, W. X.; Shen, Z.; Lin, F.; Sun, Y. J.; Min, D. L.; Tang, L. N.; He, A. N.; Yao, Y. (2012). "Comparison of the efficacy and safety of EFGR tyrosine kinase inhibitor monotherapy with standard second-line chemotherapy in previously treated advanced non-small-cell lung cancer: A systematic review and meta-analysis". Asian Pacific journal of cancer prevention : APJCP 13 (10): 5177–5182. doi:10.7314/APJCP.2012.13.10.5177. PMID 23244131. edit
17. Li Z, Xu M, Xing S, Ho W, Ishii T, Li Q, Fu X, Zhao Z (2007). "Erlotinib Effectively Inhibits JAK2V617F Activity and Polycythemia Vera Cell Growth". J Biol Chem 282 (6): 3428–32. doi:10.1074/jbc.C600277200. PMC 2096634. PMID 17178722.
18. Dudek A, Kmak K, Koopmeiners J, Keshtgarpour M (2006). "Skin rash and bronchoalveolar histology correlates with clinical benefit in patients treated with gefitinib as a therapy for previously treated advanced or metastatic non-small cell lung cancer". Lung Cancer 51 (1): 89–96. doi:10.1016/j.lungcan.2005.09.002. PMID 16290256.
19. Román Pérez-Soler, M.D., et al. (2004). "Selected Highlights". Lung Cancer Frontiers 22 (16): 3238–3247.
20. Thomas L. Petty, M.D. (2003). "Determinants of Tumor Response and Survival With Erlotinib in Patients With Non—Small-Cell Lung Cancer". Journal of Clinical Oncology 1 (17): 3–4.
21. Ren, S; Li, Y; Li, W; Zhao, Z; Jin, C; Zhang, D (2012). "Fatal asymmetric interstitial lung disease after erlotinib for lung cancer". Respiration 84 (5): 431–5. doi:10.1159/000339508. PMID 22889962.