

1 **Title Page**

2 **Title: Eruptive seborrheic keratoses induced by oral esomeprazole: A coincidental finding or**
3 **linked pathogenesis?**

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27 Abstract

28 Aim:

29 Eruptive **seborrhoeic** keratoses are characterized by rapid onset of multiple **seborrhoeic** keratoses.
30 They can be associated with internal malignancies, inflammatory dermatoses and drug reactions. Our
31 aim was to present a case with eruptive **seborrhoeic** keratoses appeared during treatment with oral
32 esomeprazole and to discuss possible etiopathogenesis.

33 Presentation of case:

34 Herein we report a 24-year-old female patient with eruptive **seborrhoeic** keratoses appeared during 1-
35 year treatment with oral esomeprazole.

36 Discussion and Conclusion:

37 Although, the association between esomeprazole treatment and eruptive **seborrhoeic keratoses** may
38 be a coincidence, previously reported growth factor changes in both conditions may be pointing out a
39 linked pathogenesis.

40 **Keywords:** eruptive **seborrhoeic** keratoses; esomeprazole; Leser-Trélat sign; epidermal growth factor.

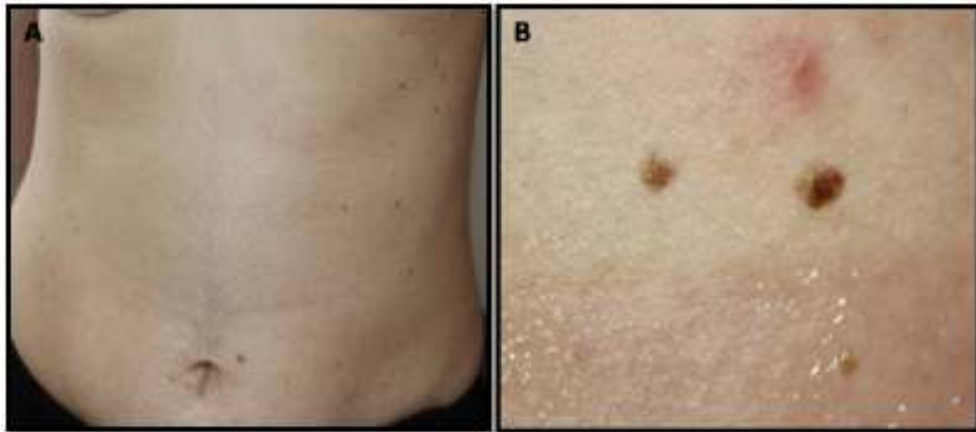
41 Introduction

42 Eruptive **seborrhoeic** keratoses are characterized by large numbers of **seborrhoeic** keratoses that
43 developed simultaneously and abruptly over a short time period on previously normal skin. The
44 etiology of eruptive **seborrhoeic** keratoses is not clear, however connection with malignancies,
45 erythroderma and various drugs has been reported [1, 2]. To the best of our knowledge, previously,
46 no association with esomeprazole treatment was reported. Herein we report **a female patient** with
47 eruptive **seborrhoeic** keratoses developed during treatment with oral esomeprazole treatment.

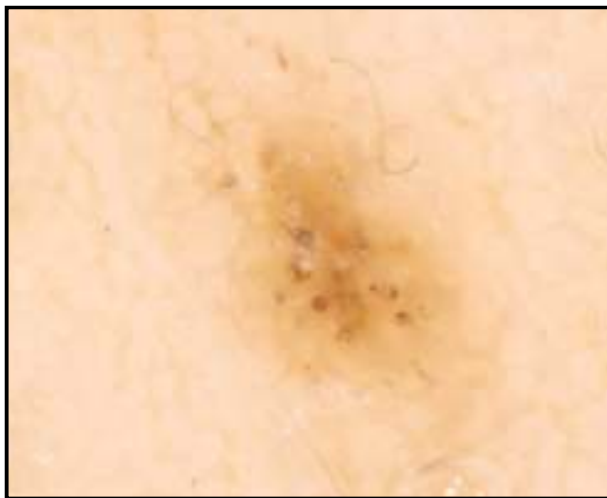
48 Case

49 A 24-year-old female presented with multiple eruptive pigmented lesions on trunk that developed
50 within the last year following 1-year treatment with oral esomeprazol (20 mg/day) used for
51 gastroesophageal reflux. The other medical and drug history were unremarkable. On physical
52 examination at least 50 pigmented stuck-on appearing papules especially located over lateral trunks
53 were detected (**Figure 1A, B**). Dermoscopic examination revealed comedo-like openings on brownish
54 background and rare milia-like cysts (**Figure 2**). Histopathological examination revealed mild epidermal
55 hyperkeratosis, acanthosis and horn cysts, which were consistent with the diagnosis of seborrhoeic

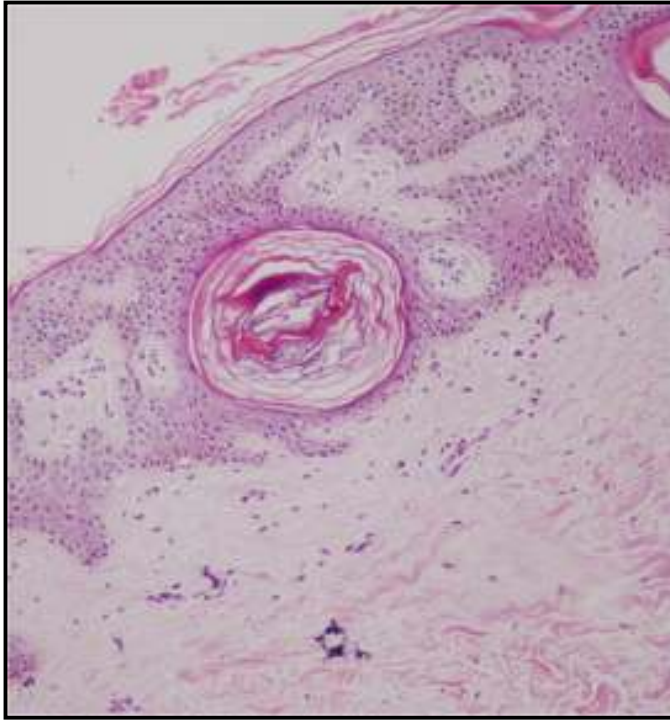
56 keratosis (Figure 3). Further examinations including complete blood count, routine blood chemistries,
57 peripheral smear, cancer-screening tests, further gastrointestinal and pelvic work-up did not reveal any
58 abnormality and anti-HIV antibody was negative. In the follow-up of 6 months, no signs of cancer have
59 developed. An informed consent for publication was obtained from the patient.



60
61 **Figure 1.** A, B: Multiple brown-black coloured, stuck-on appearing papules over the trunk.



62
63 **Figure 2.** Comedo-like openings on a brownish background and rare milia-like cysts on dermoscopy
64 (Heine Delta 20 plus nonpolarised dermatoscope, Heine Optotechnik, Herrsching, Germany; original
65 magnification: $\times 10$).



66

67 **Figure 3.** Mild epidermal hyperkeratosis, acanthosis, and epidermal cysts filled with keratin (HE×100).

68 Discussion

69 Eruptive **seborrheic** keratoses have been reported with malignancies especially in elderly patients
 70 representing Leser-Trélat sign [1]. Commonly associated malignancies include gastrointestinal tract
 71 adenocarcinomas, hematopoietic neoplasms, breast, renal and lung cancers [3-5]. They have also
 72 been reported in association with inflammatory skin conditions (erythroderma due to pityriasis rubra
 73 pilaris, psoriasis, eczema, sunburn and eczematous drug eruptions), human immunodeficiency virus
 74 infection and surgery [1, 5, 6]. Furthermore eruptive seborrheic keratoses have been rarely
 75 associated with anti-tumor necrosis factor-alpha (TNF- α) agents such as adalimumab and efalizumab,
 76 however exact etiopathogenesis has not been reported [1, 6].

77 Pathogenesis of eruptive seborrheic keratoses is not clear, however role of epidermal growth factors
 78 such as transforming growth factors and melanocyte-derived growth factors acting on keratinocytes
 79 has been proposed [3, 4].

80 **Esomeprazole is a proton pump inhibitor. It was previously reported that 14 individuals taking proton**
 81 **pump inhibitors reported seborrheic keratosis to the Food and Drug Administration between January**

2004 and October 2012. However, there is no previous data about association between eruptive seborrhoeic keratoses and oral esomeprazole [7].

Exact effects of proton pump inhibitors on tumours are not known exactly. Recently, in a study investigating the effects of oral esomeprazole on molecular pathways in ethanol-induced gastric animal model, it was shown that platelet derived growth factor-beta and nerve growth factor were significantly increased and inflammatory cytokines (IL-6, IL-8 and TNF- α) were significantly decreased after esomeprazole administration [8]. These growth factor changes may explain a possible association between esomeprazole treatment and eruptive seborrhoeic keratoses. However, in recent years there are also ongoing studies about antitumour effects of proton pump inhibitors. There is ongoing evidence that various cancers have proton pumps and intracellular pH influences cancer progression. And it has been shown that proton pump inhibition may have antitumour effects by inhibiting tumor growth and metastasis, and inducing reversion of resistance to chemotherapy [9-11].

In conclusion, in this report eruptive seborrhoeic keratoses following oral esomeprazole therapy have been described. Although this association may be a coincidence, possible changes in growth factors and inflammatory cytokines may be playing role in etiopathogenesis. The exact effects of proton pump inhibitors on tumours need to be clarified with further research.

Declaration of interest

The authors report no declarations of interest.

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