Leser-Trelat sign: Eruptive seborrheic keratoses and primary lung adenocarcinomas with an epidermal growth factor receptor mutation

August Mathien, BS,[a] and Drew Kuraitis, MD, PhD[a,b]

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INTRODUCTION

Seborrheic keratoses (SKs) are common, benign neoplasms estimated to develop on the skin of 88% of adults aged 64 years and older.[1] Eruption of numerous SKs can be a paraneoplastic phenomenon due to a visceral malignancy, which was first described by surgeons Edmund Leser and Ulysse Trelat, and was thus termed the Leser-Trelat sign (LTS).[2] Many reports of LTS document the coexistence of SKs with a visceral malignancy. Given the prevalence of SKs, there is a high likelihood of coexistence with visceral malignancies that usually affect older individuals and many of these reports may not be documenting a true paraneoplastic phenomenon.[2]

Abbreviations used:

EGFR:	epidermal growth factor receptor
LTS:	Leser-Trelat sign
SK:	seborrheic keratoses
TGF-α:	transforming growth factor-α

CASE REPORT

A 58-year-old woman presented for evaluation of eruptive lesions on her back, abdomen, thighs, and arms that appeared suddenly 6 months prior. Individual lesions were of a similar size, and she denied any that were particularly tender, pruritic, or rapidly growing. She had been applying topical antifungal creams without any improvement. Physical examination revealed hundreds of monomorphic, slightly scaly, flat-topped whitish papules over the trunk and extremities, sparing the face, palms, and soles (Fig 1). There were neither appreciable textural changes of the palms or soles nor were there any textural changes or discoloration to the axillae and neck, or otherwise any obvious rashes or abnormal skin lesions. Her nail plates were free of pitting and dystrophy. No excoriations were noted to the lesions in question. Dermoscopy was unrevealing, demonstrating hypopigmented papules with skin lines throughout (Fig 2). A punch biopsy was performed of a representative lesion and the histopathologic findings were consistent with SK. The patient denied a history of SKs or otherwise any textured papules on her body.

This patient was up-to-date with age-appropriate cancer screenings; however, due to a recent trauma, a computed tomography scan had been performed and lung nodules were identified. With concern for a paraneoplastic process, further work-up was encouraged and sampling revealed 2 invasive adenocarcinomas, one in each lung. The patient was then diagnosed with the LTS. Genetic testing of tumor specimen revealed an epidermal growth factor receptor (EGFR) T790M mutation. Further genetic testing on whole blood revealed that the patient was heterozygous for the same mutation. She later underwent surgical resection of lung tumors. Seven

From the Department of Dermatology, Roswell Park Comprehensive Cancer Center, Buffalo, New York[a]; and Department of Dermatology, Tulane University, New Orleans, Louisiana.[b]

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Correspondence to: Drew Kuraitis, MD, PhD, Department of Dermatology, Tulane University, 1430 Tulane Ave #8036, New Orleans, LA 70112. E-mail: dkuraiti@tulane.edu.

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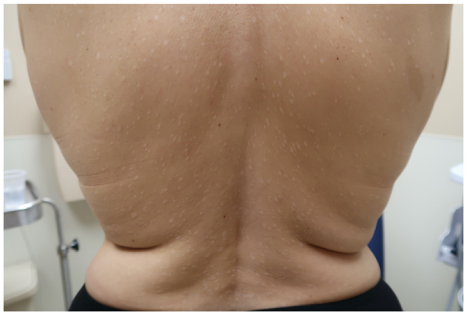

Fig 1. Monomorphic whitish, slightly scaly papules distributed over the back.

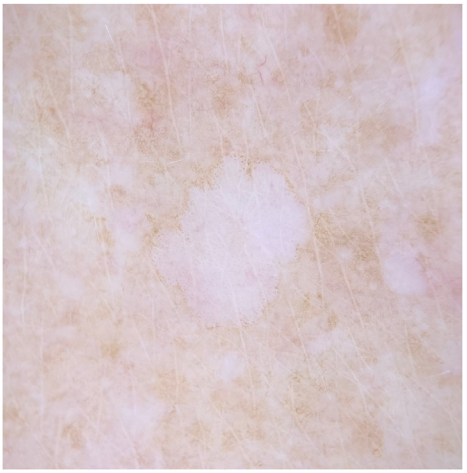

Fig 2. Dermoscopy of representative lesions, demonstrating bland, flat-topped hypopigmented papules.

months after surgery, skin lesions were still present. At that time, imaging did not suggest further development of any new pulmonary malignancies.

DISCUSSION

SKs are present on the majority of adults.[1] Although ubiquitous, the sudden eruption of SKs should prompt concern for an underlying malignancy. SKs tend to be waxy, brown papules of varying shapes and sizes. In this case of LTS, there is an eruption of monomorphic, hypopigmented, atypical SKs in the same stage of evolution, presenting around the same time as multiple primary EGFR T790M mutation-related lung adenocarcinomas. This synchronous appearance is further supportive of a paraneoplastic phenomenon.

Numerous genetic mutations have been identified in SKs. Most commonly, fibroblast growth factor receptor-3 mutations have been observed, but EGFR mutations have also been demonstrated.[3] Due to the epidermal proliferation of some paraneoplastic conditions, and the presence of EGFR throughout proliferating keratinocytes, EGFR has been hypothesized to be involved in LTS, as well as in acanthosis nigricans, another paraneoplastic phenomenon.[4] Three studies have evaluated EGFR staining in SKs obtained from LTS patients and have shown intense EGFR staining throughout lesional epidermis, although control SKs will also demonstrate a high degree of EGFR staining.[4-6] In one patient, EGFR staining intensity within SKs was reduced after surgical management of the patient's malignancy, suggesting malignancy as a driving force for EGFR expression and SK development.[4]

The EGFR T790M mutation observed in our patient is well known to be an oncogenic driver for lung adenocarcinoma and can be acquired or germline.[7] To date, it has not been reported to be associated with SKs or LTS. An acquired somatic EGFR T790M variant may be observed after administration of anti-EGFR medications, but the patient presented had never been treated with such an agent. Rather, the patient presented was found to have an EGFR T790M germline variant, which is an oncogene that carries an estimated risk of 31% for lung cancer in carriers that have never smoked and represents less than 1% of all lung adenocarcinomas.[8] The germline variant may be a weak oncogene that requires a second activating factor for oncogenesis to occur.[8]

After establishing our patient's heterozygosity for the oncogene germline mutation, in accordance with the two-hit hypothesis, it is plausible that a second "hit" may be required for oncogenesis as she has carried the first hit throughout her life and until presentation, has neither had a history of SKs nor a history of lung adenocarcinoma. This second hit may be represented by an unknown soluble factor, which would explain the rapid development of multiple primary lung malignancies at the same time as numerous SKs throughout the body, or perhaps a second acquired mutation in lung and skin. Although second activating mutations have been observed in EGFR T790M lung adenocarcinomas,[8] it would be unusual for an acquired mutation to occur at the same time throughout multiple regions of lung tissue and throughout the skin at the same time. Ellis et al proposed in 1987 that an activating soluble factor that may be responsible for the LTS is transforming growth factor-α (TGF-α), as it binds to the EGFR and it has been found at higher levels in the urine of one LTS patient.[4] If a soluble factor is required for the second hit, potential secretory sources include the developing visceral tumor, another primary tumor, or a second activating mutation. An acquired somatic mutation, as previously mentioned, would be unlikely to occur in cutaneous and lung tissues at the

same time, but it is possible that a distant somatic mutation could lead to the generation of said soluble factor, leading to synchronous tumor development in the skin and in multiple regions of the lungs. Our patient did not have any other known tumors or malignancies at the time of presentation. We were unable to assess urine levels of TGF-α in our patient.

Given the synchronous development of multiple primary lung adenocarcinomas and numerous atypical appearing seborrheic keratoses in this patient with LTS, it is reasonable to assume that there was an inciting event. The patient presented is heterozygous for an EGFR mutation that is well known to be oncogenic with respect to lung adenocarcinoma. Although the EGFR T780M mutation has not yet been associated with SKs or LTS, EGFR mutations are seen in SKs, and SKs from LTS patients also display robust staining of EGFR. In this patient, we hypothesize that a second, unidentified hit to her heterozygosity led to her synchronous presentation of eruptive SKs with multiple primary lung adenocarcinomas. Likely due to the rarity and perhaps underdiagnosis of this sign, genetic links between visceral malignancies and SKs have not been widely studied. This report serves as a reminder that the LTS is an eruption of SKs in the context of malignancy and highlights the potential genetic link between eruptive SKs and malignancy. Visceral malignancies should be considered in patients who have truly eruptive SKs, especially those with eruptive, atypical, monomorphic lesions without a known history of SKs.

Conflict of interest

None disclosed.

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