

Leser-Trélat Sign Presenting in a Patient With Recurrent Pre-B-Cell Acute Lymphocytic Leukemia

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The presence of multiple seborrheic keratoses appearing abruptly in association with an underlying malignancy is known as Leser-Trélat sign, a rare paraneoplastic cutaneous syndrome. Although this finding is most commonly associated with solid organ tumors, it also can be a clue for the presence of underlying hematologic malignancies. We present a unique case of Leser-Trélat sign in a 20-year-old man who experienced a relapse of pre-B-cell acute lymphocytic leukemia (ALL) that was previously treated with multiple courses of chemotherapy and external radiation therapy. The patient was admitted for a new cycle of chemotherapy with etoposide and cyclophosphamide and was noted to have an eruption of yellowish brown papules and plaques over his upper body. Biopsy of a representative lesion was consistent with seborrheic keratosis. A large number of rapidly appearing seborrheic keratoses is an uncommon finding in young patients and should be considered clinically suspicious as a potential indicator of Leser-Trélat sign. A thorough history and physical examination should be performed in patients presenting with this sign to rule out possible internal solid organ and hematologic malignancies.

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Leser-Trélat sign is the abrupt appearance and rapid increase in size of many seborrheic keratoses in association with an underlying malignancy, the most common being gastrointestinal tract adenocarcinomas.¹ It is an uncommon finding to see Leser-Trélat sign associated with hematologic malignancies or relapsing malignancy. Before a diagnosis of Leser-Trélat sign can be made, it is important to confirm the identity of the seborrheic keratoses histologically.² We report a patient who presented with classic features of Leser-Trélat sign associated with pre-B-cell acute lymphocytic leukemia (ALL) relapse.

Case Report

We report a 20-year-old man with a history of pre-B-cell ALL previously treated with multiple courses of chemotherapy and external radiation therapy. Because his pre-B-cell ALL recurred, the patient was admitted for a new cycle of etoposide and cyclophosphamide. On admission, he was noted to have an eruption of yellowish brown papules and plaques over his upper back, upper arms, head, and neck. The skin lesions developed approximately 1 month prior to admission and the patient denied having any preceding skin lesions.

Physical examination revealed a tired-appearing young man with multiple yellowish brown, waxy, stuck-on appearing papules and plaques over his upper back and arms (Figure 1). There were many smaller and flatter papules over his lateral neck and peripheral scalp as well as many tan to brown macules over his face. A shave biopsy of one of the papules from the back was consistent with seborrheic keratoses (Figure 2).

Additionally, in both of the patient's axillae there were well-demarcated plaques with verrucous tan peripheries and more macerated centers. These lesions were tender and had an overlying moist white



Figure 1. Multiple yellowish brown, waxy, stuck-on appearing papules and plaques were present over the patient's upper back and arms.

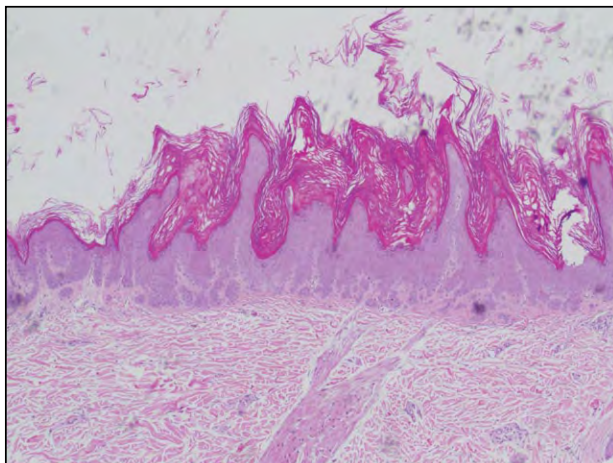


Figure 2. A shave biopsy of a papule from the patient's back was consistent with seborrheic keratoses (H&E, original magnification $\times 40$).

material that was easily scraped away to reveal beefy erythematous bases. There also was less severe erythema and maceration at the bilateral groins as well as some erythema and moist hyperkeratosis of the scrotum. A potassium hydroxide preparation performed on skin scraped from the right axilla plaque revealed numerous hyphae and yeast forms consistent with *Candida*.

Comment

There continues to be considerable debate in the literature about the validity of Leser-Trélat sign. Some argue that given that cancer and seborrheic keratoses are common in elderly people, it is too difficult to definitively establish a relationship between the 2 findings.³ It is suggested that because elderly patients are more prone to developing malignancies, the association with seborrheic keratoses is merely coincidental.⁴ However, the rapid increase in

number and size of seborrheic keratoses and their coexistence with other well-recognized paraneoplastic conditions has been recorded in more than 110 cases.⁵ A literature review from the last 3 years alone (according to a PubMed search of articles indexed for MEDLINE using the term *Leser-Trélat*) reveals 8 prior reports of Leser-Trélat sign in association with various malignancies (Table).

Our patient deserves special attention because the seborrheic keratoses appeared in a 20-year-old man with no history of skin disorders, an occurrence that is exceptionally rare among young individuals. Additionally, our patient had acanthosis nigricans of the bilateral axillae and groins, a condition that sometimes accompanies Leser-Trélat sign.¹ These areas were found to be secondarily colonized with *Candida* and responded well to topical therapy. Together, these findings support the theory that the association of the cutaneous findings and underlying malignancy is not merely coincidental.

Additionally, 2 other findings in this case deserve special attention and are unique discoveries in

Leser-Trélat Sign Associated With Various Malignancies

Reference (Year)	Type of Malignancy
Yavasoglu et al ⁶ (2011)	Acute myeloid leukemia
Constantinou et al ⁷ (2010)	Adenocarcinoma of colon
Kluger and Guillot ⁸ (2009)	Adenocarcinoma of prostate
Bölke et al ⁹ (2009)	Ovarian cancer
da Rosa et al ⁹ (2009)	Adenocarcinoma of prostate
Dasanu and Alexandrescu ¹⁰ (2009)	Adenocarcinoma of lung
Li et al ⁵ (2009)	Nasopharyngeal carcinoma
Siedek et al ¹¹ (2009)	Malignant melanoma
Current report (2011)	Recurrent pre-B-cell acute lymphocytic leukemia

themselves. First, the onset of multiple seborrheic keratoses in this patient happened rapidly, within weeks of his malignancy's relapse, whereas traditionally, the keratoses occur as an initial presentation of cancer. Second, the patient's seborrheic keratoses appeared in association with a hematologic malignancy as opposed to a solid organ tumor, which is more typically seen. Considered collectively, this case supports the validity of Leser-Trélat sign, as it illustrates a conclusive finding of multiple seborrheic keratoses in a patient with a documented underlying malignancy.

In addition to the empirical evidence, there continues to be mounting immunohistochemical evidence that Leser-Trélat sign is well-founded. It has long been proposed that an increase in circulating agents related to the underlying tumor contributed to the cutaneous findings. Examples of these agents include transforming growth factor α and epidermal growth factors.¹² Normally, epidermal growth factor receptors are present on basal keratinocytes and decrease as the keratinocytes differentiate in the upper epidermal layers. Immunohistochemical testing has documented an increase in the expression of epidermal growth factor receptors in the basal keratinocytes and upper epidermal layers of a patient whose history is consistent with Leser-Trélat sign.¹³

Hafner et al¹⁴ demonstrated increased expression of mutated growth factor receptors in seborrheic keratoses.¹⁴ Specifically, mutations of fibroblast growth factor receptor 3 in the epidermis have been shown to be involved in the development of seborrheic keratoses.^{14,15} A likely explanation for the association between malignancy and the rapid appearance of multiple seborrheic keratoses is that the underlying malignancy contributes to an activating mutation in fibroblast growth factor receptor 3. It also may produce a growth factor–like inducer that acts as a ligand for the mutated keratinocyte receptor, predisposing certain individuals to increased frequency of seborrheic keratoses.

Conclusion

This unique case is a valuable addition to the current literature and further supports the validity of Leser-Trélat sign. It provides a documented example of the association between a large number of abruptly appearing, rapidly growing, histologically confirmed seborrheic keratoses in a young man with an underlying pre-B-cell ALL. It is likely that the level of required investigation for an underlying malignancy is related to the quantity and speed at which the seborrheic keratoses develop. Although no specific number of seborrheic keratoses can definitively determine when a malignancy workup is indicated, certain factors such as the patient demographics, medical

history, and presence of constitutional signs and symptoms should be considered in the decision of when to proceed with additional screening utilizing computed tomography or other modalities. It is imperative that Leser-Trélat sign be considered when a patient presents with these findings, and a thorough history and physical examination should be performed, keeping in mind the possibility of a hematologic malignancy.

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