

COVID-19 infection and Leser-Trelat sign: is there an association?

Farhad Handjani¹, roya radanfar², Mozhdeh Sepaskhah³, and niloofar Ebrahimi²

¹ Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran Department:

²Shiraz University of Medical Sciences

³1- Department of Dermatology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

April 7, 2023

COVID-19 infection and Leser-Trelat sign: is there an association?

Farhad Handjani^{ab}, Roya Radanfar^{ab}, Mozhdeh Sepaskhah^{ab*}, Niloofar Dehdari Ebrahimi^c

^aMolecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

^bDepartment of Dermatology, Shiraz University of Medical Sciences, Shiraz, Iran

^cStudent Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

*corresponding author

Abstract

Seborrheic keratosis is a typical benign skin lesion that is almost always seen in elderly populations. Sudden onset and rapid increase in size and/or number of seborrheic keratoses is called the Leser-Trélat sign, suggesting a paraneoplastic appearance of internal malignancy. However, eruptive seborrheic keratoses are also described in some non-malignant conditions such as human papillomavirus infection and human immunodeficiency virus infection.

Herein, we describe a patient with eruptive seborrheic keratoses after recovery from COVID-19 infection with no evidence of internal malignancy.

This case was partially presented as a poster in the 102 nd Annual Congress of British Association of Dermatologists in Glasgow, Scotland from July 5th to 7th 2022.(1).

The patient signed written informed consent to permit the publication of the case report without identifying data and to use the photography for publication. The researchers committed to maintaining patient confidentiality. Institutional ethics committee approved the case report (ethics code: IR.sums.med.rec.1400.384).

Key learning point:

The etiology of the Leser-Trélat sign is unknown, it is likely that viral infections like COVID-19 can be associated with eruptive seborrheic keratosis,, although the exact pathogenesis is still not clear.

Introduction

Covid-19 infection is caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], a Beta coronavirus. The most common clinical manifestations of COVID-19 are respiratory symptoms. As the

pandemic progressed, other aspects were discovered, including cutaneous manifestations of the disease for example erythematous rash, urticaria, vesicle formation, and purpura. (2).

To date, no report has been made of the sudden eruption of seborrheic keratoses following COVID-19 infection.

Sudden onset and rapid increase in size and/or number of seborrheic keratoses is called the Leser-Trélat sign, suggesting a paraneoplastic appearance of internal malignancy,(3). The most frequently associated malignancies are adenocarcinoma of the colon, stomach, lung, or breast, although the Leser-Trélat sign has also been reported in non-malignant conditions, e.g., lepromatous leprosy, (4), erythrodermic pityriasis rubra pilaris, (5), human immunodeficiency virus infection,(6), and human papillomavirus infection.(7,). Leser-Trélat sign can also occur in healthy individuals in the absence of internal malignancy. (8). Herewith, we report a case of eruptive seborrheic keratoses, which presented after recovery from COVID-19 infection in a 50-year-old man.

Case report

A 50-year-old man presented to our dermatology clinic complaining of sudden appearance of multiple wart-like lesions on his back which had occurred two months after recovery from COVID-19 infection.

According to his medical history, the patient presented with cough, fever, and dyspnea about two months prior to the appearance of his skin lesions. He was referred to a health center where a nasopharyngeal swab was taken, and his PCR test for COVID-19 was positive. In addition, bilateral patchy ground-glass infiltration was reported in his high-resolution computed tomography (HRCT) scan in favor of COVID-19 infection. The patient was then treated with acetaminophen, dexamethasone (intramuscular injection), salmeterol, and fluticasone inhaler, and his symptoms improved.

Two months after recovery from mild COVID-19 infection, several small asymptomatic pigmented verrucous papules appeared on the patient's back. Physical examination revealed multiple rough, oval-shaped, brownish papules varying in size from 2 mm in diameter to 15×5×2 mm (Figure 1). Dermatoscopy of the lesions was also performed. Both clinical and dermoscopic findings were in favor of seborrheic keratosis (Figure 2). In order to reach a final diagnosis, a skin biopsy was requested, and microscopic examination of the biopsy specimen showed hyperkeratosis, well-defined epidermal hyperplasia, composed mainly of the proliferation of benign-looking basaloid cells and fewer squamoid cells, horn cysts, and increased melanin, mostly in the dermo-epidermal junction. The dermis showed no significant change (Figure 3). Based on the above findings, the patient was diagnosed with eruptive seborrheic keratosis.

To determine the possible cause of this eruption, the patient was further evaluated. In his past medical history, he was generally healthy before his COVID-19 infection and had no history of co-morbidities. The patient was then examined to rule out any internal malignancies. Laboratory tests revealed normal results and included a complete blood count (white blood cells 5300/mm³, red blood cells: 4.5×10^6 /mm³, platelets: 152000/mm³), liver and kidney function tests, electrolytes, prostate-specific antigen, and urine analysis. Gastrointestinal endoscopy and colonoscopy ruled out any gastrointestinal malignancy. Chest X-ray and high-resolution computed tomography (HRCT) scan revealed no malignant lesion. In addition, the patient's abdominopelvic sonography was normal. The patient had no family history of similar skin lesions and gave no history of any chronic inflammatory skin diseases or viral conditions. Therefore, the appearance of the Leser-Trélat sign after COVID-19 infection could be regarded as a possibility in this patient.



Fig. 1. Small pigmented verrucous papules on the patient's back

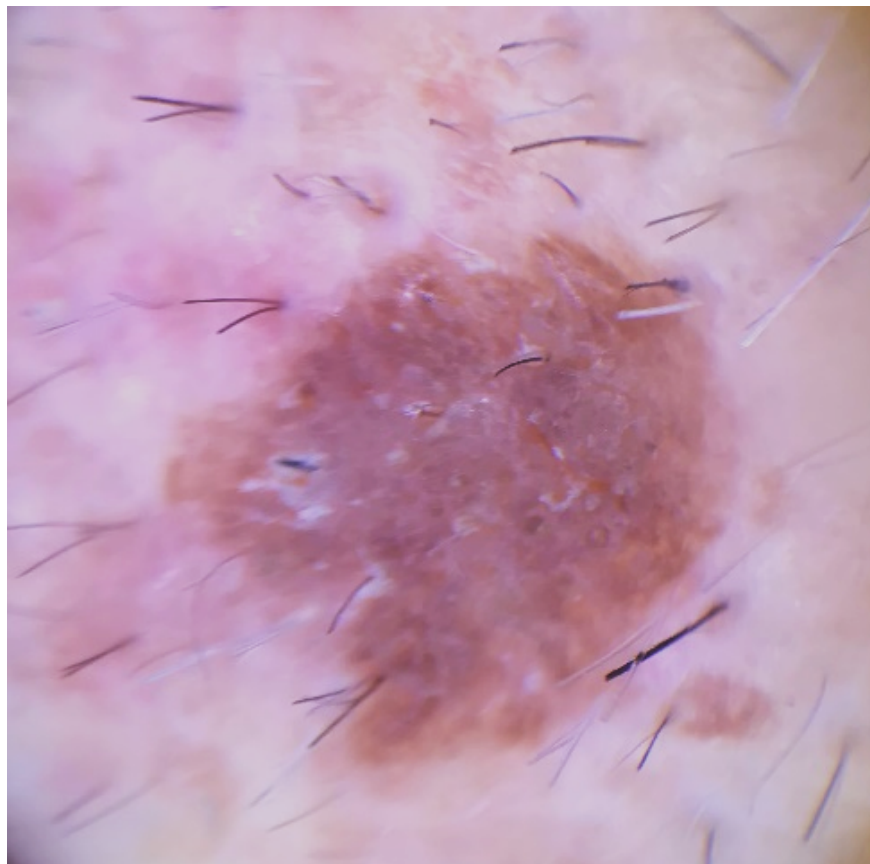


Fig. 2. Dermoscopic examination revealed a brown lesion with milia-like cysts, brown dots, and multiple comedone-like openings.

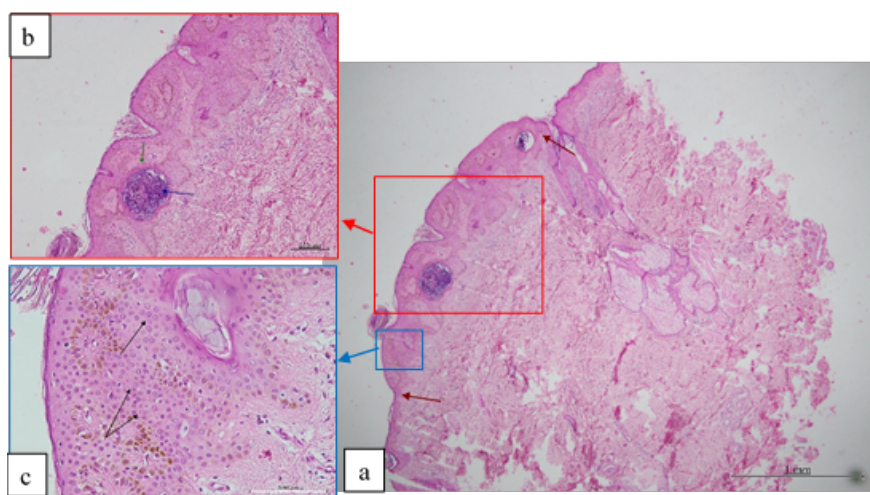


Fig. 3. Histopathology examination: a) Hyperkeratosis, well-defined epidermal hyperplasia (defined between red arrows), and horn cysts (hematoxylin and eosin stain, 40 ×); b) Hyperkeratosis, epidermal hyperplasia, horn cyst (blue arrow), surrounded by basaloid cells (green arrow), and basal melanosis (hematoxylin and

eosin stain, 100 ×); c) Epidermal acanthosis, predominantly composed of basaloid cells (black arrows) and some squamoid cells. Increased melanin is seen mostly in the dermo-epidermal junction (hematoxylin and eosin stain, 400 ×).

Discussion

The etiology of the Leser-Trélat sign is still unknown, although it has been considered as a paraneoplastic phenomenon. Some cases with the Leser-Trélat sign have occurred in non-malignant patients, including patients with underlying infections like viral infections (7), lepromatous leprosy, (4), in association with erythrodermic pityriasis rubra pilaris, (5). In addition, a case has been reported in a heart transplant patient treated with immunosuppressive drugs (9).

In addition, some observations have indicated that the Leser-Trélat sign may develop following viral infections. Inamadar and Palit (6) have reported a case with human immunodeficiency virus infection who developed the Leser-Trélat sign. In a study by Tsambaos et al., human papillomavirus (HPV) DNA was positive in 34 patients from among 173 cases with non-genital seborrheic keratosis. (7).

Some theories have associated its development to transforming growth factor-alpha and epidermal growth factors secreted from tumor cells. According to previous studies, TGF-alpha is overexpressed in seborrheic keratosis, and it may play a significant role in the progression and increase in the number of seborrheic keratoses. (10-11). It has been shown that COVID-19 infection with lung injury can induce expression of transforming growth factor, (12), so there is the possibility of a similar mechanism in our patient, although severe lung findings were not reported. However Leser-Trélat sign is usually associated with a variety of immune suppression conditions such as malignancy or viral infection, so development of eruptive seborrheic keratosis may be due to immunosuppression situation caused by COVID-19 infection. and not exactly due to TGF- alpha .

Immunohistochemical analysis has also revealed an increased expression of tumor necrosis factor-alpha (TNF-alpha) in seborrheic keratosis skin lesions (13), which is in accordance with increased inflammatory cytokines such as TNF-alpha observed in COVID-19 patients. (14).

Although the development of Leser-Trélat sign in healthy persons does not fully support the theories of TNF- alpha and TGF-alpha and immunosuppression conditions .

Therefore, it is likely that viral infections like COVID-19 can be associated with eruptive seborrheic keratosis, although the exact pathogenesis is still not clear.

Conflicts of interest statement:

The authors have no conflicts of interest to declare .All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

References

1. P11: Leser-Trélat sign: can it follow COVID-19 infection? *British Journal of Dermatology*. 2022;187(S1):35-6. doi: <https://doi.org/10.1111/bjd.21133>.
2. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34(5):e212-e3. doi: 10.1111/jdv.16387. PubMed PMID: 32215952.
3. Bennett CN, Schmieder GJ. Leser Trelat Sign. StatPearls. Treasure Island (FL): StatPearls Publishing
- Copyright © 2021, StatPearls Publishing LLC.; 2021.
4. D'Souza M, Garg BR, Reddy BS, Ratnakar C. Lepromatous leprosy with extensive truncal seborrheic keratoses and acral verruca vulgaris. *Int J Dermatol*. 1994;33(7):498-500. doi: 10.1111/j.1365-4362.1994.tb02864.x. PubMed PMID: 7928035.

5. Schwengle LE, Rampen FH. Eruptive seborrheic keratoses associated with erythrodermic pityriasis rubra pilaris. Possible role of retinoid therapy. *Acta Derm Venereol.* 1988;68(5):443-5. PubMed PMID: 2461032.
6. Inamadar AC, Palit A. Eruptive seborrheic keratosis in human immunodeficiency virus infection: a coincidence or 'the sign of Leser-Trélat'? *Br J Dermatol.* 2003;149(2):435-6. doi: 10.1046/j.1365-2133.2003.05463.x. PubMed PMID: 12932267.
7. Tsambaos D, Monastirli A, Kapranos N, Georgiou S, Pasmatzis E, Stratigos A, et al. Detection of human papillomavirus DNA in non-genital seborrheic keratoses. *Arch Dermatol Res.* 1995;287(6):612-5. doi: 10.1007/bf00374085. PubMed PMID: 7487151.
8. Safa G, Darrieux L. Leser-Trélat Sign without Internal Malignancy. *Case Rep Oncol.* 2011;4(1):175-7. Epub 20110329. doi: 10.1159/000327363. PubMed PMID: 21526136; PubMed Central PMCID: PMC3081649.
9. Hsu C, Abraham S, Campanelli A, Saurat JH, Piguet V. Sign of Leser-Trélat in a heart transplant recipient. *Br J Dermatol.* 2005;153(4):861-2. doi: 10.1111/j.1365-2133.2005.06850.x. PubMed PMID: 16181485.
10. Ellis DL, Kafka SP, Chow JC, Nanney LB, Inman WH, McCadden ME, et al. Melanoma, growth factors, acanthosis nigricans, the sign of Leser-Trélat, and multiple acrochordons. A possible role for alpha-transforming growth factor in cutaneous paraneoplastic syndromes. *N Engl J Med.* 1987;317(25):1582-7. doi: 10.1056/nejm198712173172506. PubMed PMID: 2825016.
11. ΣΗΕΝΓ Ω-Ξ, ΞΙΑΟ Η-Λ, ΣΟΝΓ Τ. Εξπρεσσιον οφ Τρανσφορμινγ Γρωωτη Φαστορ-α ιν Σκιν Λεσιονς οφ Σεβορρηεις Κερατοσις. Τηε ηινεσε Θουρναλ οφ Δερματοενερεολογψ. 2004:09.
12. Φερρειρα-Γομες Μ, Κρυγλο Α, Δυρεκ Π, Ηεινριςη Φ, Τιζιαν ΄, Ηεινζ ΓΑ, ετ αλ. ΣΑΡΣ-δ΄-2 ιν σεερε ΄Ο΄ΙΔ- ινδυσες α ΤΓΦ-β-δομινατεδ ζηρονις ιμμυνε ρεσπονσε τηατ δοες νοτ ταργετ ιτσελφ. Νατ δμμυν. 2021·12(1):1961. Επυβ 20210330. doi: 10.1038/s41467-021-22210-3. ΠυβΜεδ ΠΜΙΔ: 33785765· ΠυβΜεδ έντραλ ΠΜ΄ΙΔ: ΠΜ΄ΠΜ΄8010106.
13. ηεν ΞΨ, Ψαν ΒΞ, Μαν ΞΨ. ΤΝΦα ινηιβιτορ μαψ βε εφφεστιε φορ σεερε ΄Ο΄ΙΔ-19: λεαρνινγ φρομ τοξις επιδερχαλ νεςρολψσις. Τηερ Αδ Ρεσπιρ Δις. 2020·14:1753466620926800. doi: 10.1177/1753466620926800. ΠυβΜεδ ΠΜΙΔ: 32436460· ΠυβΜεδ έντραλ ΠΜ΄ΙΔ: ΠΜ΄ΠΜ΄7243041.
14. Manaka L, Kadono S, Kawashima M, Kobayashi T, Imokawa G. The mechanism of hyperpigmentation in seborrheic keratosis involves the high expression of endothelin-converting enzyme-1alpha and TNF-alpha, which stimulate secretion of endothelin 1. *Br J Dermatol.* 2001;145(6):895-903. doi: 10.1046/j.1365-2133.2001.04521.x. PubMed PMID: 11899142.

