Diagnostic Microbiology and Infectious Disease 95 (2019) 89–92

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

A rare case of malignant syphilis after adalimumab therapy due to Crohn's disease associated with bariatric surgery

Incilay Kalay Yıldızhan [a,*], Hatice Erdi Şanlı [a], Hülya Çetinkaya [b], Bengü Nisa Akay [a], Pelin Koçyiğit [a], Nihal Kundakçı [a]

[a] Department of Dermatology, Ankara University School of Medicine
[b] Department of Gastoenterology, Ankara University School of Medicine

ARTICLE INFO

Article history:
Received 27 January 2019
Received in revised form 5 March 2019
Accepted 20 April 2019
Available online 21 June 2019

Keywords:
Malignant syphilis
Adalimumab
Crohn's disease
Bariatric surgery

ABSTRACT

Malignant syphilis (also known lues maligna) is a rare and severe variant of secondary syphilis. It is most commonly seen in patients who are infected with human immunodeficiency virus (HIV), and rarely, it can occur in immunocompetent individuals. The exact mechanism of the development of malignant syphilis is not clear. It could probably be associated with immunosuppression, inappropriate immune response of the host, or virulent strain of *Treponema pallidum*. Coexistence of immunosuppression and inappropriate immune response may predispose to develop malignant syphilis in HIV-infected patients with immune reconstitution inflammatory syndrome. Herein, we report the first case of malignant syphilis after adalimumab therapy for Crohn's disease due to bariatric surgery and discuss the underlying possible pathogenic mechanisms.

1. Introduction

Malignant syphilis is clinically characterized by erythematous papules, nodules, and ulcerative lesions covered with thick rupoid crusts accompanied by systemic symptoms such as high fever, asthenia, myalgia, and arthralgia (Yanagisawa et al., 2011). The disease has a progressive course similar to neoplasms. Therefore, the diagnosis can be sometimes challenging for clinicians. Factors predisposing to the development of malignant syphilis are chronic alcoholism, malnutrition, immunosuppressant drugs, and coexistent debilitating diseases (Rao et al., 2017). Anti–tumor necrosis factor (TNF) agents suppress the physiologic response to TNF, which is part of the inflammatory response. These agents have several cutaneous side effects. Herein, we report a case of malignant syphilis after adalimumab therapy for Crohn's disease due to bariatric surgery.

2. Case report

A 29-year-old female presented with a 4-week history of fever; joint pain; and an extensive, painful, and pruritic erythematous papulonodular rash affecting her face, trunk, and extremities. She also complained of general malaise, headache, and myalgia. She had a sleeve gastrectomy operation 3 years ago and Crohn's disease developed 1 year after bariatric surgery. The patient was given adalimumab therapy due to severe Crohn's disease which was unresponsive to conventional therapies. After the ninth injection, fever, arthralgia, and tender skin lesions occurred. The eruptions had started as papular and nodular lesions and progressed to painful nodular ulcerations. Physical examination revealed erythematous, ulcerated papulonodular lesions with varying sizes ranging from 0.5 to 2 cm on her face, neck, trunk, and arms. The ulcers were punched out, well circumscribed, and covered with adherent scale crust (Fig. 1). Oral and genital mucosae were not involved. A biopsy was taken with the differential diagnosis of pyoderma gangrenosum, disseminated deep fungal infection, pityriasis lichenoides et varioliformis acuta (PLEVA), generalized necrotic herpes zoster, lymphomatoid papulosis, and primary cutaneous anaplastic T-cell lymphoma. The skin biopsy reveals an epidermal ulceration, basal cell degeneration, and predominantly lymphohistiocytic infiltrate which extends into the deep dermis. The vessels showed reactive endothelial changes and vasculopathy without fibrinoid necrosis. These clinical and histological findings suggested a diagnosis of PLEVA.

HIV serology was nonreactive. Full blood cell count was normal. The erythrocyte sedimentation rate and C-reactive protein levels were significantly increased. Antibiotic (metronidazole, ciprofloxacin), antiviral (valacyclovir), and antifungal (amphoterisin) therapies were initiated by the Infectious Disease Department because of fever of unknown origin. There was no improvement with these therapies. Staining and cultures for bacteria, mycobacteria, and fungi were negative. During follow-up, the crusts covering the ulcers turned into thick laminated rupoid crusts which were a specific feature of malignant syphilis

* Corresponding author. Tel.: +90-312-5082231.
E-mail address: incilaykalay@gmail.com (I.K. Yıldızhan).

https://doi.org/10.1016/j.diagmicrobio.2019.04.009
0732-8893/

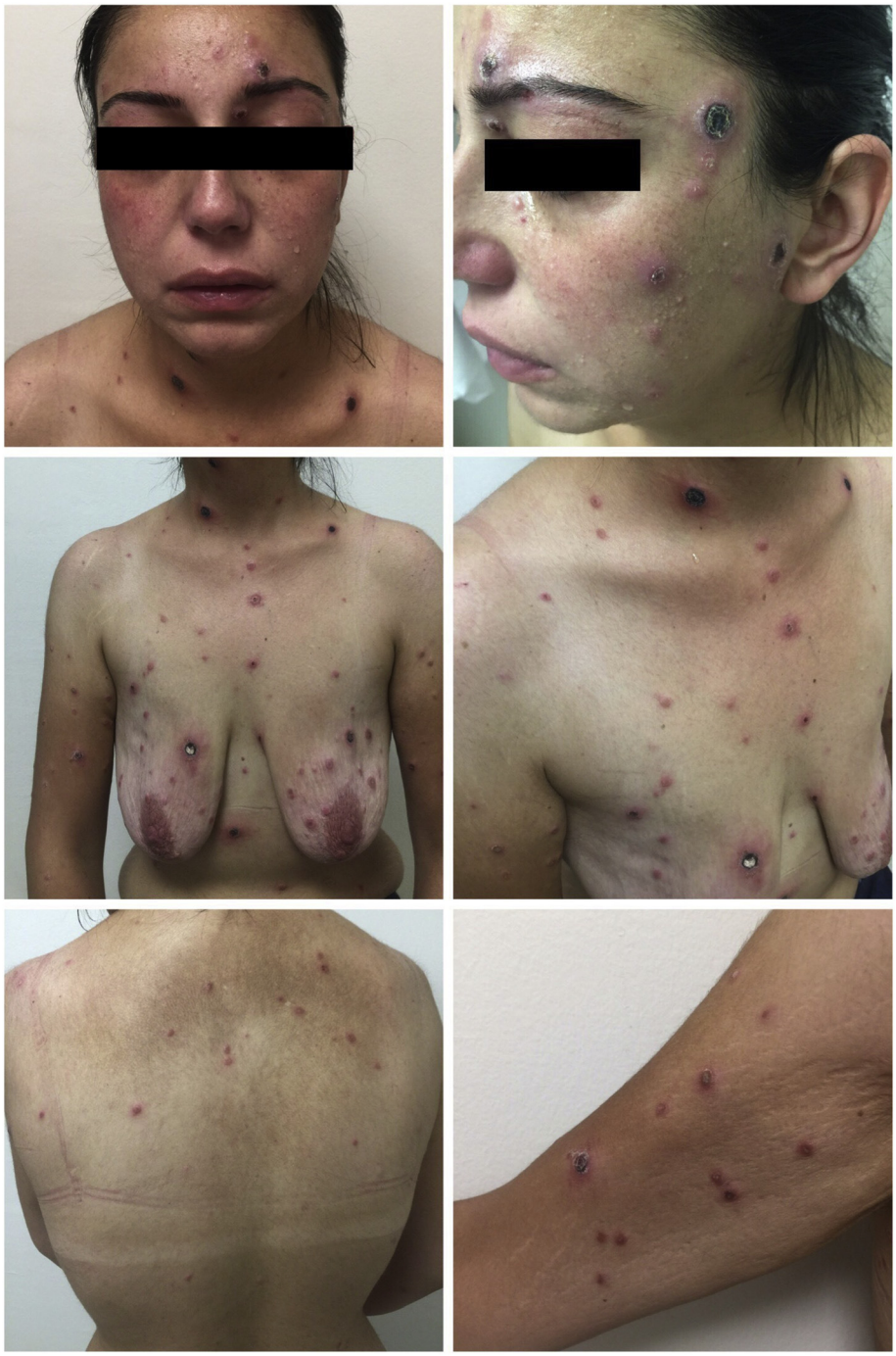

Fig. 1. Erythematous ulcerated papules and nodules of varying sizes on the face, neck, trunk, and proximal part of arms. The ulcers were well circumscribed, deep seated, and covered with adherent crust with an erythematous halo.

(Fig. 2). Venereal Disease Research Laboratory test gave a reactive result at the 1:16 dilution.

The diagnosis of syphilis was confirmed by *positive Treponema pallidum* hemagglutination test. The patient was treated with intramuscular benzathine penicillin G 2.4 million units weekly for 3 consecutive weeks. Jarish–Herxheimer reaction was observed. Clinical response was rapid; the ulcers healed with atrophy and hypopigmentation (Fig. 3).

3. Discussion

Malignant syphilis is an unusual ulcerative variation of secondary syphilis. It usually occurs from 6 weeks to 1 year after primary infection. The lesions typically begin as papules, which quickly evolve to ulcers with central necrosis and that are covered by rupoid crusts. It rarely affects oral mucosa and palmoplantar area unlike secondary syphilis (Yanagisawa et al., 2011). The lesions are usually accompanied by fever, lymphadenopathy, headaches, myalgia, and visual complaints (Yanagisawa et al., 2011). Diagnostic criteria which were described by Fisher et al. include compatible gross and microscopic morphology, a high titer of positivity in serologic tests for syphilis, Jarish–Herxheimer reaction following treatment, and dramatic response to antibiotic therapy (Fisher et al., 1969). The intramuscular injection of benzathine penicillin G 2.4 million units weekly for 3 consecutive weeks is the recommended treatment option for malignant syphilis.

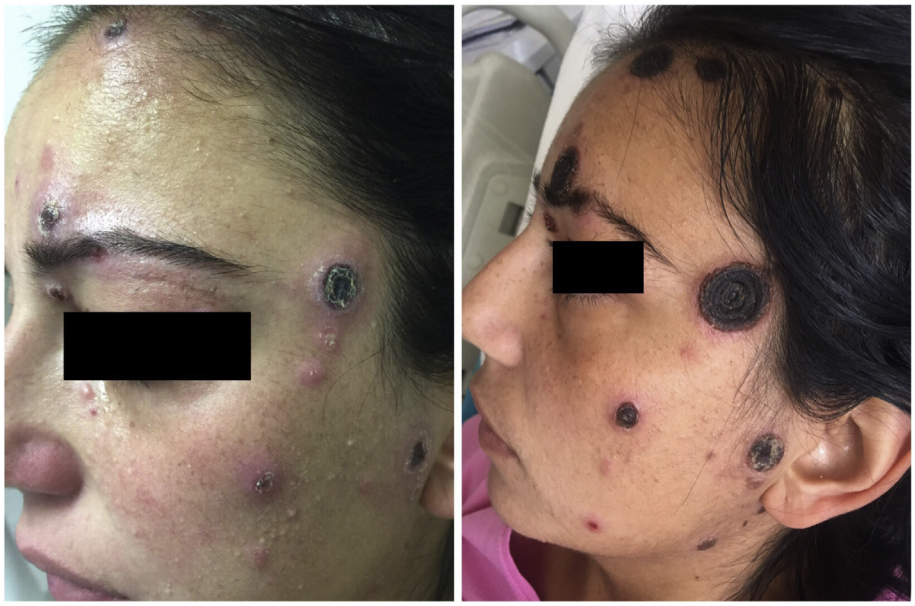

Fig. 2. One week after hospitalization, the crusts covering the ulcers turned into thick laminated rupoid crusts.

Poor health, malnutrition; widespread use of antibiotics and corticosteroids; and, most importantly, the presence of HIV infection may predispose development of malignant syphilis (Tucker et al., 2009). However, it can rarely be seen in immunocompetent individuals (Rao et al., 2017). The underlying mechanisms for development of malignant syphilis are not clear. It can be the result of immunosuppression, inappropriate immune response of the host, and a virulent strain of *Treponema pallidum* (Bahmer and Anton-Lamprecht, 1983).

The frequency of malignant syphilis in HIV-infected patients is 60 times higher than in the general population (Schofer et al., 1996). HIV

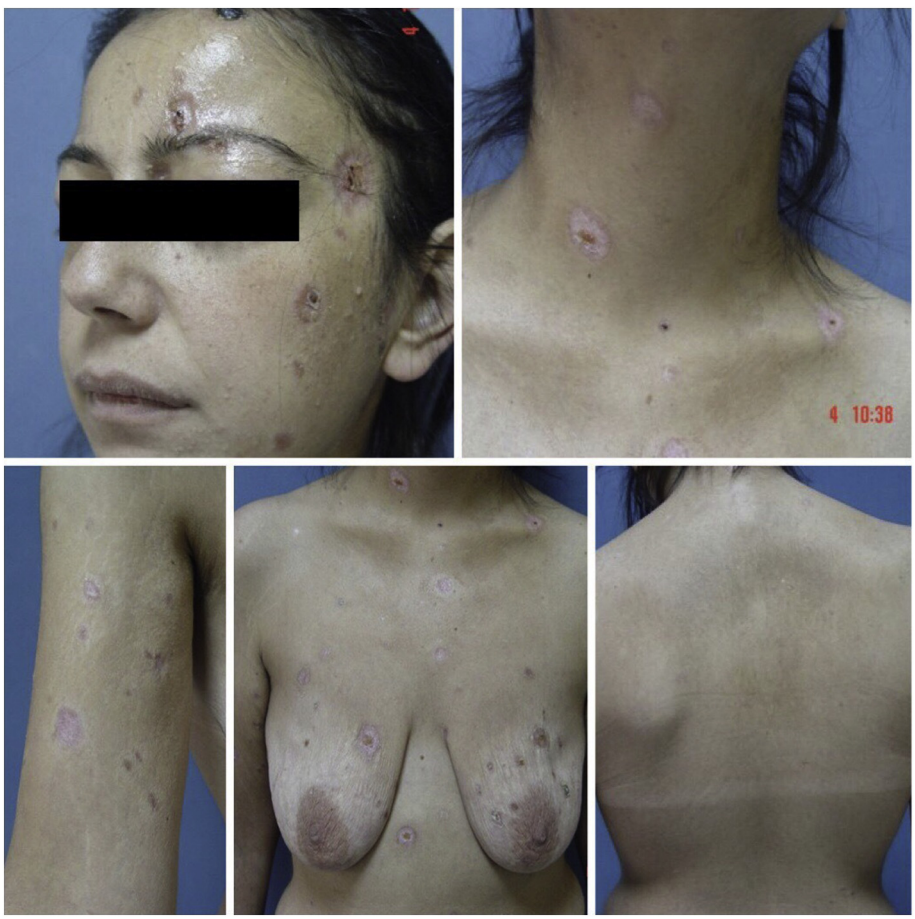

Fig. 3. The ulcers healed with atrophy and hypopigmentation after treatment.

infection may reduce the immunological response to treponemal infection through a decrease in cell-mediated immunity. However, it has been reported that immune reconstitution inflammatory syndrome (IRIS) increases the risk of development of malignant syphilis in HIV-infected patients (Braue et al., 2015). IRIS is characterized by atypical exuberant inflammation and an accelerated clinical presentation suggesting a restoration of antigen-specific immunity after antiretroviral therapy (Bosamiya, 2011). Increased CD4 T lymphocyte count is one of the minor criteria for IRIS and responsible for clinical presentation. In addition to immunosuppression, altered immune response may have been resulted with atypical clinical manifestations of malignant syphilis.

Development of inflammatory bowel disease (IBD) after bariatric surgery is very rare (Canete et al., 2018). It remains unknown why bariatric surgery triggers the development of IBD. It may be associated with the induction of exaggerated intestinal inflammation due to anatomical changes which cause dysbiosis and/or mucosal barrier dysfunction in genetically predisposed patients, or a massive release of proinflammatory cytokines during rapid weight loss from fat tissue (Cottam et al., 2004).

Multiple potential complications and adverse effects of targeted TNF-α inhibition have been identified. Because these agents modulate the immune system, not unexpectedly, a number of infectious adverse events have been observed, and chief among them is mycobacterial infections. However, malignant syphilis in association with anti-TNF therapy for IBD has not been reported previously. Anti-TNF agents suppress the physiologic response to TNF, which is part of the inflammatory response.

In conclusion, we think that the suppressive effects of adalimumab therapy to inflammatory response leading to inappropriate immune response and proinflammatory cytokines released after bariatric surgery may trigger the development of malignant syphilis similar to HIV-infected patients with IRIS. Physicians should keep in mind malignant syphilis when confronted with papulonodular lesions covered with rupoid crusts in patients who are under anti-TNF therapies for inflammatory conditions.

Acknowledgment

None.

Disclosure of interest

The authors report no conflicts of interest.

References

Bahmer FA, Anton-Lamprecht L. Ultrastructural features of malignant syphilis and demonstration of Treponema pallidum. Int J Dermatol 1983;22(3):165–70. PubMed PMID: 6343268.

Bosamiya SS. The immune reconstitution inflammatory syndrome. Indian J Dermatol 2011;56(5):476–9. https://doi.org/10.4103/0019-5154.87114. PubMed PMID: 22121257; PubMed Central PMCID: PMCPMC3221202.

Braue J, Hagele T, Yacoub AT, Mannivanan S, Sokol L, Glass F, et al. A case of rupioid syphilis masquerading as aggressive cutaneous lymphoma. Mediterr J Hematol Infect Dis 2015;7(1), e2015026. https://doi.org/10.4084/MJHID.2015.026. PubMed PMID: 25960854; PubMed Central PMCID: PMCPMC4418386.

Canete F, Manosa M, Clos A, Cabre E, Domenech E. Review article: the relationship between obesity, bariatric surgery, and inflammatory bowel disease. Aliment Pharmacol Ther 2018;48(8):807–16. https://doi.org/10.1111/apt.14956. PubMed PMID: 30178869.

Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, et al. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obes Surg 2004;14(5):589–600. https://doi.org/10.1381/096089204323093345. PubMed PMID: 15186624.

Fisher DA, Chang LW, Tuffanelli DL. Lues maligna. Presentation of a cas and a review of the literature. Arch Dermatol 1969;99(1):70–3. PubMed PMID: 5761808.

Rao AG, Swathi T, Hari S, Kolli A, Reddy UD. Malignant syphilis in an immunocompetent adult male. Indian J Dermatol 2017;62(5):524–7. https://doi.org/10.4103/ijd.IJD_733_16. PubMed PMID: 28979018; PubMed Central PMCID: PMCPMC5618843.

Schofer H, Imhof M, Thoma-Greber E, Brockmeyer NH, Hartmann M, Gerken G, et al. Active syphilis in HIV infection: a multicentre retrospective survey. The German AIDS Study Group (GASG). Genitourin Med 1996;72(3):176–81. PubMed PMID: 8707318; PubMed Central PMCID: PMCPMC1195645.

Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. Sex Transm Dis 2009;36(8):512–4. https://doi.org/10.1097/OLQ.0b013e3181a2a946. PubMed PMID: 19455078.

Yanagisawa N, Ando M, Imamura A, Akagi K, Horiguchi S, Suganuma A, et al. Pathologically confirmed malignant syphilis in an HIV-infected patient. Intern Med 2011;50(20):2423–6. PubMed PMID: 22001480.