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Case Report

Severe Cutaneous Manifestation of Malignant Syphilis in a Patient with Behçet's Uveitis: A Case Report

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Keywords
Behçet's disease · Case report · Lues maligna · Malignant syphilis · Panuveitis · Syphilis

Abstract
Introduction: Syphilis exhibits a wide range of clinical presentations, mimicking various systemic and ocular diseases. Ocular syphilis, in particular, manifests with multiple presentations, ranging from anterior uveitis to panuveitis, making it a potential differential diagnosis for Behçet's uveitis. Here, we present a unique case of Behçet's panuveitis that was undergoing immunomodulatory therapy and was complicated by ocular syphilis. Notably, this case also featured rare cutaneous manifestations associated with secondary syphilis, commonly known as malignant syphilis. ***Case Presentation:*** A 38-year-old Thai man with refractory end-stage Behçet's panuveitis reported a maculopapular rash accompanied by increased intraocular inflammation. The escalation of immunomodulatory therapy, intended to manage the provisional diagnosis of active ocular and cutaneous Behçet's disease, resulted in clinical deterioration, with the rash transforming into multiple noduloulcerative lesions. Despite negative serologic tests for syphilis at baseline before initiating immunomodulatory therapy, syphilis infection was eventually diagnosed following reevaluation and the observation of spirochetes in a skin biopsy specimen. The patient was treated with intravenous penicillin G, resulting in an improvement in intraocular inflammation and resolution of noduloulcerative rashes. ***Conclusion:*** Intraocular inflammation and mucocutaneous lesions in syphilis can mimic the presentation of Behçet's disease. The introduction of immunomodulatory therapy may alter the clinical

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picture, leading to a severe and atypical presentation. A high index of suspicion for reevaluating serologic tests or performing tissue biopsies is warranted for an accurate diagnosis.

Introduction

Syphilis, often referred to as "the great imitator," is notorious for its wide range of clinical presentations that mimic various systemic and ocular diseases [1, 2]. In the past decade, the resurgence of syphilis has emerged as a significant public health concern. Its incidence has increased considerably, with a 78.9% rise in total cases reported in the USA between 2018 and 2022 [3, 4]. Syphilis is classified into stages according to the duration of infection and the presenting symptoms [2]. Cutaneous manifestations of secondary syphilis encompass a wide spectrum of clinical presentations. In rare cases, a severe form known as "malignant syphilis" emerges, predominantly affecting individuals in an immunocompromised state. This group includes patients with conditions such as HIV, alcoholism, malnutrition, diabetes mellitus, or those receiving immunosuppressive therapy [5].

Skin lesions in malignant syphilis were described as nodules with central necrotic ulcers, sometimes accompanied by rupioid crusting [5–7]. Given the ongoing increase in syphilis infections among immunosuppressed individuals, recognizing these atypical cutaneous manifestations becomes a diagnostic challenge. In this context, we present a case highlighting a severe manifestation of secondary syphilis with concurrent syphilitic uveitis in a patient undergoing immunosuppressive therapy for refractory Behçet's disease.

Case Presentation

A 38-year-old man with refractory end-stage Behçet's uveitis was being treated at the uveitis clinic of Siriraj Hospital, a tertiary center in Thailand, for the past decade. Prior to the initiation of his immunomodulatory therapy, serologic tests for infectious etiologies, including syphilis, were conducted, all of which returned negative. His ongoing medication regimen consisted of monthly subcutaneous injection of 50 mg golimumab, weekly subcutaneous injection of 25 mg methotrexate, 7.5 mg daily oral prednisolone, and alternate day application of prednisolone acetate 1%.

Following the administration of the 56th dose of golimumab, the patient returned for a follow-up with complaints of decreased vision and the presence of ill-defined erythematous plaques with some erythematous pustular papules, primarily distributed across the trunk, neck, and extremities (Fig. 1a, b). Visual acuity decreased from 6/38 to 6/76 in the right eye and from 6/60 to 6/120 in the left eye. A slit-lamp examination revealed fine keratic precipitates, grade 2+ anterior chamber cells, and grade 1+ anterior vitreous cells in both eyes. The fundus examination showed a vitreous haze of grade 0.5+ vitreous haze, with a mild pale optic disc, vascular attenuation, and old gliotic vessels. No retinitis or active vasculitis was detected in either of the eyes.

A consultation with a dermatologist was sought to address the emergence of new-onset rashes. The provisional diagnosis pointed toward relapsed Behçet's disease, coinciding with active intraocular inflammation. Consequently, oral prednisolone was increased to 30 mg/day,

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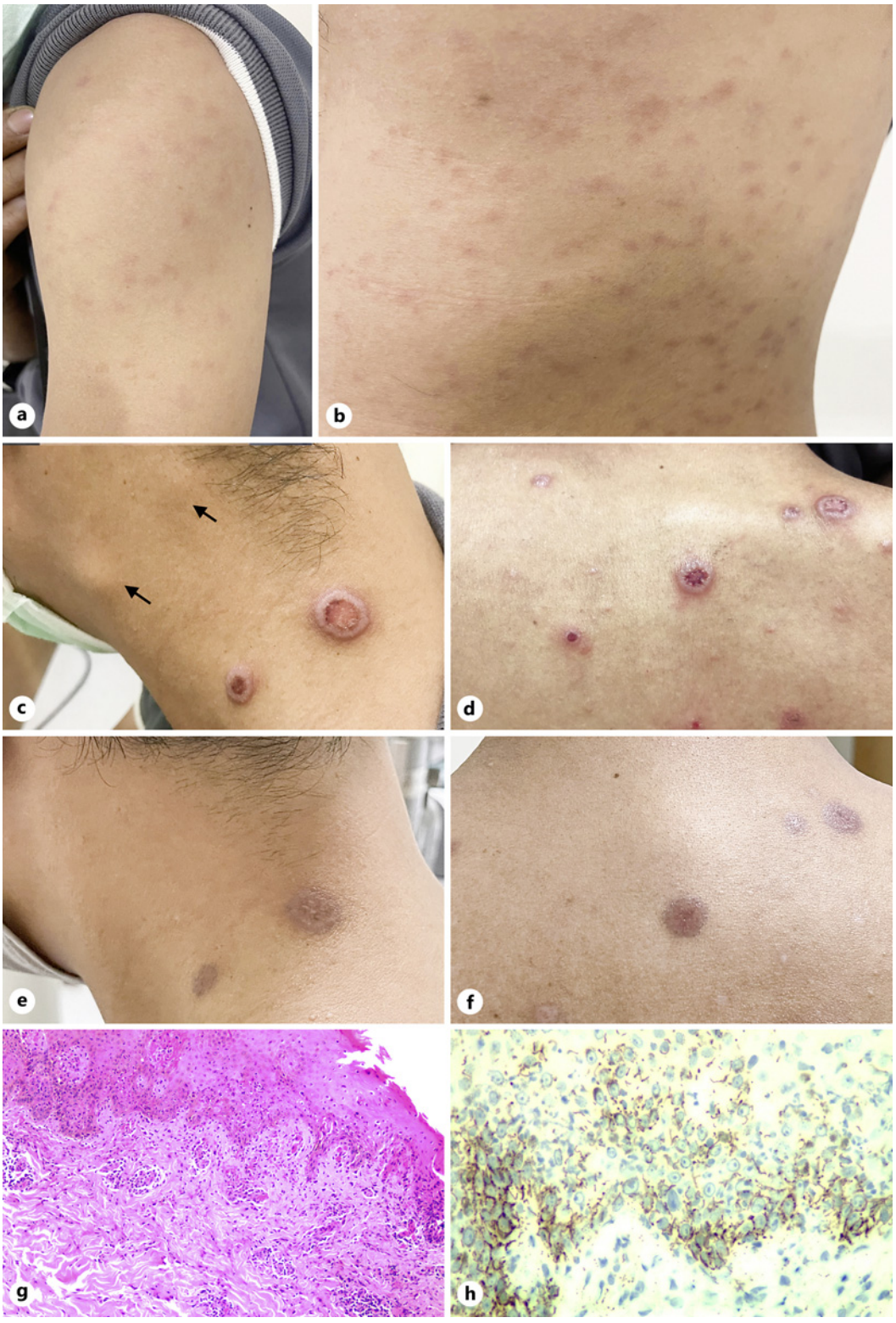

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methotrexate was switched to azathioprine, golimumab treatment continued, and prednisolone acetate 1% was administered four times daily.

Upon a 4-week follow-up, the anterior chamber revealed grade 1+ cells with grade 0.5+ vitreous haze in both eyes. Fundus examination did not reveal any new lesions. However, initially reported erythematous rashes had become multiple discrete erythematous indurated nodules with central ulceration, distributed over the back, head, and forehead. In addition, multiple palpable lymph nodes measuring up to 1.5 cm in size were detected within the posterior cervical and occipital regions (Fig. 1c, d).

The differential diagnosis initially included an infectious granuloma. Therefore, a skin biopsy was performed for culture and histopathology examination, accompanied by laboratory investigations to rule out possible opportunistic infections. Subsequent physical examination findings revealed the existence of multiple round flat genital scars. The patient disclosed a history of unsafe sex and multiple genital ulcers that had developed 1 month prior to the onset of erythematous rashes.

Laboratory results indicated a reactive Venereal Disease Research Laboratory (VDRL) test with a titer of 1:32 and a positive *Treponema pallidum* Hemagglutination Test (TPHA). The cryptococcus antigen and anti-HIV test yielded negative results. A chest radiograph revealed no infiltrations and urinalysis was normal. Consequently, a diagnosis of secondary syphilis with syphilitic uveitis was established. The patient was admitted, and an intravenous regimen of 4 million units of penicillin G was initiated every 4 h. Prednisolone was reduced to 15 mg/day, while golimumab and azathioprine were discontinued.

Given the patient's immunosuppressed state, there was concern about neurosyphilis. Consequently, a lumbar puncture was performed and a cerebrospinal fluid analysis showed a white blood cell count of 1 cell/mm^3, a protein level of 31 mg/dL, and a glucose level of 48 mg/dL. The cerebrospinal fluid VDRL test yielded a nonreactive result.

During the admission period, both intraocular inflammation and skin lesions demonstrated marked response to intravenous penicillin therapy. The tissue scraping for Gram staining, potassium hydroxide preparation, and acid-fast bacteria staining showed no evidence of organisms, while bacteria, fungi, and mycobacteria cultures revealed no growth. The skin biopsy revealed epidermal erosion with perivascular and periadnexal infiltration by neutrophils, eosinophils, and plasma cells. Overall histopathology was nonspecific; however, an increase in plasma cells with edematous vessels raised the possibility of syphilis. *T. pallidum* immunostaining was positive for numerous spirochetes at the dermoepidermal junction (Fig. 1g, h). The Ziehl-Neelsen, Gomori methenamine silver, and periodic acid Schiff stains are negative for organisms. These findings were consistent with a clinical diagnosis of malignant syphilis or lues maligna, a severe atypical cutaneous manifestation of secondary syphilis.

After completing a 2-week course of penicillin treatment, the ulcerative nodules began to flatten and develop scales, accompanied by resolution of the lymphadenopathy (Fig. 1e, f). The eye examination demonstrated an improvement in visual acuity, returning to the baseline level of the patient of 6/24 in the right eye and 6/76 in the left eye. The anterior chamber

Fig. 1. At the initial presentation, ill-defined erythematous papules distributed across the arm (**a**) and back (**b**). **c**, **d** Four weeks later, the rashes transformed into multiple discrete erythematous indurated nodules with central ulceration. Posterior cervical and occipital lymphadenopathy was observed (black arrows). **e**, **f** Two weeks after receiving intravenous penicillin G, the ulcerative nodules began to flatten, accompanied by the resolution of the lymphadenopathy. **g** Epidermal erosion with perivascular and periadnexal infiltration by neutrophils, eosinophils, and plasma cells is noted. No basal vacuolar interface change is identified (H&E ×100). **h** Immunohistochemistry for Treponema staining was positive for numerous spirochetes at the dermoepidermal junction.

showed rare cell grading. Fundus examination and optical coherence tomography of the macula revealed an improvement in vitreous haze, and findings consistent with end-stage Behçet's uveitis remained unchanged in both eyes (Fig. 2). The VDRL titer decreased to 1:4 at the 6-month follow-up.

Discussion

The presented report demonstrated a patient with secondary syphilis with syphilitic uveitis in a patient with Behçet's disease undergoing treatment with systemic corticosteroids and immunomodulatory agents. Behçet's disease is a systemic inflammatory disease that affects multiple systems, including ocular inflammation, arthritis, oral and genital ulcers, skin lesions, and involvement of visceral organs involvement [8]. The diverse clinical presentations of Behçet's disease may overlap with those of syphilis, particularly in ocular and mucocutaneous manifestations.

Panuveitis is the most common form of ocular involvement in Behçet's disease and HIV-positive ocular syphilis, whereas posterior uveitis, particularly chorioretinitis, is the most common presentation of ocular syphilis in the general population [3, 8]. Intraocular inflammation can occur at any stage of syphilis and mimic the ocular findings of Behçet's disease, such as vitritis, retinitis, and vasculitis. In our case, active intraocular inflammation presented as an increase in anterior chamber cells and vitritis, which did not distinguish between these two diseases. Therefore, a high degree of suspicion of syphilis, combined with a compatible history and physical examination, played a crucial role in the serologic examination of syphilis.

Regarding mucocutaneous manifestations, a few case reports have demonstrated the similarity in manifestation between Behçet's disease and syphilis [9, 10]. Cutaneous lesions in Behçet's disease occur in up to 80% of patients, presented in various combinations. Common forms include papulo-vesiculo-pustular eruptions and erythema nodosum [8, 11]. The reported cutaneous manifestations of secondary syphilis vary, ranging from the typical maculopapular rash with or without scaling that can spread throughout the body or be located in a specific area such as palms and soles, to atypical forms such as nodular, annular, pustular, frambesiform or noduloulcerative rashes [7]. Without treatment, symptoms of secondary syphilis typically resolve within 2–6 weeks in untreated individuals but may recur in approximately one-fourth of cases [2]. However, our case experienced a continuous transformation of maculopapular rashes into atypical form, consistent with the noduloulcerative form of malignant syphilis.

Malignant syphilis, a severe manifestation of secondary syphilis, has been reported primarily in HIV-infected patients. This association may be related to their immunocompromised state, similar to the condition observed in our patients who received immunomodulatory therapy. The characteristics of these lesions typically involve irregularly distributed and multiple erythematous papules that subsequently evolve into well-defined round or oval necrotic ulcerated plaques on the scalp, face, trunk, and extremities. Erythematous papules and several small pustules can progress to ulcerations involving the forehead, trunk, and extremities, closely resembling the presentation in our patient. Furthermore, the onset of this eruption can be preceded by symptoms such as fever, chills, anorexia, weight loss, and severe headaches [2]. Nevertheless, these constitutional symptoms were not observed in our patient.

Regarding skin lesions, noduloulcerative rashes can share characteristics with penicilliosis, histoplasmosis, cryptococcosis, and nontuberculous mycobacterial infections which should be considered in differential diagnosis [12–15]. Consequently, histopathological findings from skin biopsies or culture specimens become a valuable tool for diagnosis if the causative organism is identified. In our patient, the skin lesions biopsied revealed positive numerous spirochetes by *T. pallidum* immunohistochemistry. However, the absence of

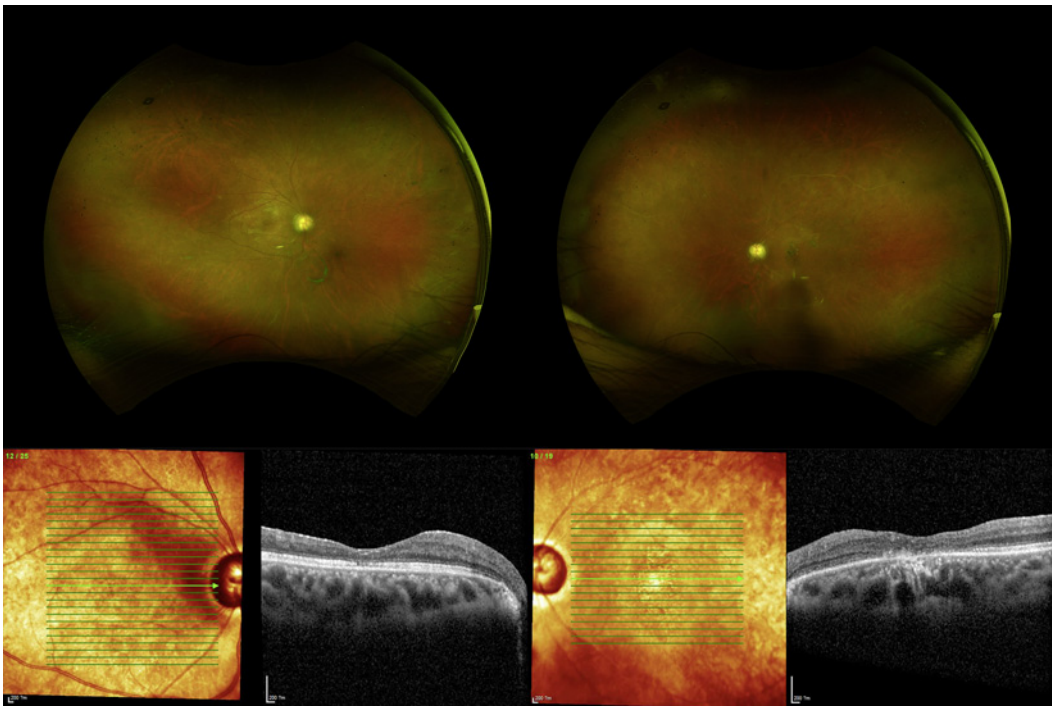

Fig. 2. Ultra-wide-field fundus imaging of both eyes (upper) reveals end-stage Behçet's uveitis, including alterations in the retinal pigment epithelium, pale disc, vascular attenuation, and gliotic vessels. A macular scar is observed in the left eye. Spectral domain optical coherence tomography of both eyes (lower) demonstrates atrophic retina with disrupted outer segments. In the left eye, hyperreflectivity corresponds with a scar at the retinal pigment epithelium-Bruch's membrane complex.

spirochetes from histopathological examination cannot definitely rule out malignant syphilis [7]. In such a case, rapid resolution of the lesions with appropriate antibiotics, as observed in our patient, is helpful in terms of therapeutic diagnosis.

In conclusion, corticosteroids and immunomodulatory therapy can alter the presentation of syphilis, giving rise to rare and severe atypical manifestations that may complicate the diagnosis and delay proper treatment. It is advisable to consider reevaluating syphilis serological tests in sexually active individuals undergoing therapy for immune-mediated disorders, especially when they encounter unexplained worsening of intraocular inflammation or exhibit symptoms suggestive of syphilis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539723).

Statement of Ethics

This study protocol was reviewed, and the need for approval was waived by the Siriraj Institutional Review Board (SIRB). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pu.C., Pi.C., and U.T. made substantial contributions to the conception and design of the work. P.S. contributed essential details regarding histopathologic results. C.L. and C.R. provided valuable insights into the skin examination. All authors participated in both the writing and revision of the manuscript. S.B. and N.T. played key roles in approving the final manuscript. The final manuscript was read and approved by all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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