Disseminated herpes zoster mimicking rheumatoid vasculitis in a rheumatoid arthritis patient on etanercept

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Abstract: Tumor necrosis factor-alpha (TNFalpha)-blocking agents are immunomodulating agents introduced for treatment of a variety of chronic inflammatory disease conditions. Adverse effects include an increased incidence of infections. Clinically, these infections often have atypical presentations that may hamper prompt diagnosis. In our report of a patient on etanercept therapy for rheumatoid arthritis, the correct diagnosis was delayed because disseminated herpes zoster was clinically mimicking vasculitis. Initially assuming rheumatoid vasculitis, immunosuppression was increased, resulting in worsening of skin lesions. Only an extended work-up, including a skin biopsy and viral cultures, established the correct diagnosis. Management of varicella zoster virus (VZV) infection primarily focuses on early initiation of antiviral therapy to control VZV replication. Therapy with intravenous acyclovir followed by oral valacyclovir allowed complete resolution of acute skin changes. In immunosuppressed patients, the possibility of infection with atypical presentation must always be kept in mind, and that this might mimic other disease conditions. Broad differential diagnosis and an extended diagnostic workup help in establishing the correct diagnosis.

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Disseminated Herpes Zoster Mimicking Rheumatoid Vasculitis in a Rheumatoid Arthritis Patient on Etanercept


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Key Words
Tumor necrosis factor-α antagonist · Etanercept · Varicella zoster virus · Rheumatoid vasculitis · Rheumatoid arthritis

Abstract
Tumor necrosis factor-α (TNFα)-blocking agents are immunomodulating agents introduced for treatment of a variety of chronic inflammatory disease conditions. Adverse effects include an increased incidence of infections. Clinically, these infections often have atypical presentations that may hamper prompt diagnosis. In our report of a patient on etanercept therapy for rheumatoid arthritis, the correct diagnosis was delayed because disseminated herpes zoster was clinically mimicking vasculitis. Initially assuming rheumatoid vasculitis, immunosuppression was increased, resulting in worsening of skin lesions. Only an extended work-up, including a skin biopsy and viral cultures, established the correct diagnosis.

Introduction
Immunomodulation employing a new class of biologic agents is increasingly being used for an expanding array of mostly chronic inflammatory autoimmune diseases. The biologic agents allegedly represent efficacious and relatively safe therapeutic agents. Nevertheless, the tumor necrosis factor-α (TNFα)-blocking agents have been connected with reactivation of a variety of infectious agents, such as mycobacterium species and viruses. In these cases, the clinical presentation and course of infection frequently are atypical. Diagnosis may therefore be delayed and needs additional steps in the work-up. Infections on TNFα antagonist therapy concern approximately one-third of etanercept-treated patients [1], including reactivation of tuberculosis as the most important, but uncommon problem [2].

We report a case of disseminated varicella zoster virus (VZV) infection clinically mimicking vasculitis in a patient on TNFα antagonist treatment with etanercept for rheumatoid arthritis (RA). Assuming rheumatoid vasculitis, immunosuppression was initially increased with worsening. Only an extended work-up, including a skin biopsy and viral cultures, established the correct diagnosis and therapy.

Case Report
A 70-year-old woman presented with multiple, partially confluent hemorrhagic bullous lesions with central necrotic areas on her left ankle, right leg, right axilla and left ear (fig. 1). Her medical history included osteoporosis, arterial hypertension, chronic alcoholism and smoking.

Four months before admission, solitary bullous lesions showed up on her dorsal left foot. The clinical differential diagnosis included fixed drug eruptions, autoimmune bullous disease and vasculitic lesions. Under the first assumption of a drug-related reaction, etanercept was withheld for 1 month. Nonetheless, the number of lesions increased and extended to the right leg, the right axilla and the left...
on set of the clinical presentation with early signs of systemic vasculitis and course in association with RA. On virological culture of skin biopsy, VZV was identified. A diagnosis of disseminated VZV infection due to reactivation was made. The patient had experienced four episodes of VZV reactivation in the past, but these VZV reactivations were strictly segmental at the time. Treatment was started with intravenous acyclovir 500 mg three times daily on 4 consecutive days, followed by oral valacyclovir 1 g three times daily for another 10 days. At regular follow-up examinations, careful debridement of larger lesions was performed and wound care with topical steroids was delivered. Finally, at 6 months all lesions were healed with residual hyperpigmentation and some tenderness.

**Discussion**

RA is a chronic inflammatory disease with extra-articular manifestations. Dermatologic manifestations include rheumatoid nodules, pyoderma gangrenosum, granulomatous dermatitis, rheumatoid neutrophilic dermatitis, and rheumatoid vasculitis. Rheumatoid vasculitis has an overall annual incidence of less than 1% [3]. Clinically, rheumatoid vasculitis presents with intracellular edema (ballooning degeneration) and acantholysis.

![Fig. 2. a Scanning magnification of an intact intra-epidermal vesicle in which the residual keratinocytes show intranuclear inclusions characteristic for herpetic viral changes. b Detailed view of acantholytic keratinocytes with intranuclear inclusions.](image_url)
sents with painless or tender, reddish to brown lesions, typically located on distal and in particular lower extremities. Also bullous lesions like hemorrhagic blisters can be found in rheumatoid vasculitis [4]. Cutaneous adverse effects of a TNFα-blocking agent therapy include infections, dermatitis, and drug-related eruptions, less commonly vasculitis, psoriasis-like eruptions, drug-induced systemic lupus erythematosus, dermatomyositis, lymphomatoid papulosis-like eruptions, and intravascular histiocytosis [5, 6].

In our case, rheumatoid vasculitis was suspected on the base of the clinical presentation with symmetrically distributed, hemorrhagic and necrotic lesions of the lower extremities and further progression after brief interruption of etanercept therapy. For this reason, etanercept treatment was reintroduced, in combination with systemic corticosteroids and methotrexate. The cutaneous lesions worsened, and a biopsy was performed. Histology revealed virotrpic epidermal changes, and virus culture identified VZV.

The development and reactivation of viral infections is well documented on TNFα-antagonist therapy [7]. In a report in 2007, the authors identified reactivation of VZV in 3% of patients on TNFα antagonists (infliximab, adalimumab, etanercept) prescribed for chronic inflammatory disease [8]. In contrast to infliximab and adalimumab, etanercept did not significantly increase the risk of herpes zoster [9]. VZV reactivations tend to be more complicated in immunocompromised patients. The incidence in the Wegener’s Granulomatosis Etanercept Trial (WGET) cohort was 45 cases per 1,000 patient-years [10]. These patients often showed disseminated infection with vesicles and other verruca-related skin manifestations at a distance from the affected dermatome. Similar to our case, atypical recurrent varicella was described in a 2008 report [11]. Prompt antiviral therapy is important to reduce the incidence of acute complications and long-term sequelae. Immunosuppressed individuals and patients over the age of 50 have a greater risk of developing postherpetic neuralgia [12]. First-line treatment of VZV infection or reactivation is systemic antiviral therapy. Management primarily focuses on early antiviral therapy and sufficient analgesic treatment [13] started within 1 week of onset of VZV symptoms or any time before full crusting of lesions [12]. In clinical practice, brivudin, famciclovir and valacyclovir have better compliance than acyclovir: oral acyclovir requires dosing every 5 h. Brivudin shows the lowest inhibiting concentration for VZV of all these drugs and needs once daily dosing only. However, in Switzerland, brivudin is not registered for use in immunosuppressed patients. Furthermore, brivudin is contraindicated in conjunction with 5-flurouracil (5-FU) because of cumulative 5-FU toxicity due to irreversible inhibition of 5-FU catabolism induced by brivudin [14].

In conclusion, we present a case of atypical presentation of disseminated VZV infection clinically mimicking vasculitis in a patient with RA on the TNFα-blocking agent etanercept. Not until an extended work-up, including skin biopsy and viral cultures, were performed was the correct diagnosis established. In immunosuppressed patients, including those on the newer TNFα inhibitors, the possibility of infection with atypical presentation must always be kept in mind, and that this might mimic other conditions. Only clinical suspicion and appropriate diagnostic procedures will promptly enable correct diagnosis and management [15].

References