

domains: Two Z-alpha domains, three dsRNA-binding domains and the putative deaminase domain, which are located in exon 2, exons 2-7 and exons 9-14 respectively [4]. The deaminase domain of the DSRAD protein is located in the codon from 886 to 1,221, which is approximately 30% of the full length of the DSRAD protein. These results suggest that the deaminase domain might be a hot spot for mutations [5]. The missense mutation c.3073A>G alters a conserved amino acid residue at 958 in exon 10, which is located in the putative deaminase domain, so the amino acid residue at 958 is suspected to play an important role in the conformation of the catalytic site of the enzyme, and the mutation at this position could probably compromise enzyme activity [6].

In conclusion, the results provide an addition to the DSH mutation database and will contribute further to the understanding of DSH genotype/phenotype correlations and to the pathogenesis of this disease. In a future study, we will construct the p.H958R mutant of DSRAD, and explore the pathogenesis of DSH. ■

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Department of Dermatology, Second Hospital of Xi'an Jiaotong University, 157 Xi Wu Road, Xi'an, Shaanxi, 710004, China  
<sup>1</sup>These authors all contributed equally to this work.  
 <Xiao\_SX@163.com>

**Yingying DONG<sup>1</sup>**  
**Shengxiang XIAO<sup>1</sup>**  
**Jianwen REN<sup>1</sup>**  
**Jia HUO<sup>1</sup>**  
**Yan LIU<sup>1</sup>**  
**Xiaoli LI<sup>1</sup>**

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## Hansen's disease in an HIV patient complicated by deep vein thrombosis: a rare complication of thalidomide therapy

A 33-year-old man HIV<sub>1</sub>-positive (born in Angola and a resident of Portugal since 1997), treated with high antiretroviral treatment (HAART) since 1999, was diagnosed with borderline leprosy, in a type 2 reaction, and was treated with multibacillary-multidrug therapy, as defined by

the WHO, in combination with prednisolone (60 mg/day). Three months later, thalidomide therapy (200 mg/day) was successfully introduced to control severe and recurrent Erythema Nodosum Leprosum (ENL). Six weeks later, the patient developed dyspnea and severe edema in both legs (*figure 1*).

Homan's sign was positive and a doppler ultrasonography revealed massive adherent thrombosis in both popliteal and femoral veins, extending to the common iliac vein. Angio-CT was consistent with pulmonary thromboembolism with pulmonary infarction. A potential prothrombotic state was excluded following analysis of erythrocyte and platelet counts, lipidemia, proteins C and S blood levels, search for resistance to activated protein C and antithrombin III levels, lupus anticoagulant, anticardiolipin or anti- $\beta_2$ -glycoprotein antibodies. Moreover, the patient did not have any other associated thrombotic risk factors, including cigarette smoking, infrequent or heavy hard drug use, immobility, malignancy, heart disease, inflammatory bowel disease, nor a history of previous thrombotic episodes.

Thalidomide therapy was discontinued and the patient was treated with subcutaneous low-molecular weight heparin (enoxaparin 80 mg b.i.d.) and oral warfarin. His condition progressively improved and, after successful anticoagulation therapy, thalidomide was safely restarted and a vena cava filter implanted. One year later the patient remains well, medicated with MB-MDT, thalidomide 200 mg/day, warfarin and prednisolone (10 mg/day).

The first reports of thrombotic complications related to thalidomide therapy were observed in a series of 5 patients, 4 with lupus erythematosus and 1 with severe atopic dermatitis (all with thrombotic risk factors) [1]. In addition, thalidomide-triggered thrombosis had been reported in patients with cicatricial pemphigoid, sarcoidosis or aphthosis and during the treatment of malignancy (multiple myeloma and renal-cell carcinoma), particularly when associated with chemotherapy [2-5]. Almost 6500 ENL patients who did not respond to other treatment drugs have been treated with thalidomide. Among them, DVT was reported in only two patients but neither had



**Figure 1.** Edema of both legs, more accentuated in the right foot with a positive Godet sign.

associated pulmonary thrombosis. The first patient received concomitant dexamethasone-cyclophosphamide pulses [4] and the second was similarly treated with prednisolone [5]. In those cases DVT developed after eight and six weeks post thalidomide therapy, respectively, but in neither case was thalidomide restarted. Interestingly, in our patient this drug was safely restarted two weeks later following successful anticoagulation therapy and one year later the patient is still being treated (with concomitant corticosteroids) without further complications. In retrospect, we recognize that it was possible in our patient that corticotherapy and HIV infection contributed to thrombosis development. In fact, Vetrichevel *et al.* recently suggested that there was a possibility of thrombosis in patients receiving thalidomide therapy together with corticosteroids *i.e.*, both drugs have a synergistic, suppressive effect on thrombomodulin because they inhibit/decrease the production of TNF- $\alpha$  [5]. Currently available epidemiological evidence also suggests that chronic HIV infection is associated with a two- to ten-fold increased risk of venous thrombosis in comparison to an age-matched control population [6]. The hypercoagulable state present in many HIV patients is associated with an increased risk of haemostatic changes and of superimposed infections. HAART has also been associated with an amplified risk of DVT by some investigators, however, the data are insufficient to support these claims [6].

This case highlights the increased thrombosis risk following thalidomide therapy in an HIV/leprosy co-infected patient without major thrombotic risk factors, even when used as an indicated treatment for ENL, and highlights the possible danger of not diagnosing DVT in an ENL patient since edema of both legs is a common occurrence during this reaction. ■

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<sup>1</sup>Dermatology Department, Curry Cabral Hospital, Rua da Beneficencia n°8, 1069-166 Lisbon, Portugal  
<sup>2</sup>Internal Medicine Department, Curry Cabral Hospital  
<sup>3</sup>Dermatopathologie, Friedrichshafen, Germany  
<sup>4</sup>Pathology Department, Curry Cabral Hospital  
<sup>5</sup>Infectious Disease Department, Curry Cabral Hospital  
<sandradmedeiros@clix.pt>

**Sandra MEDEIROS<sup>1</sup>**  
**Candida FERNANDES<sup>1</sup>**  
**Nidia MARTINS<sup>2</sup>**  
**João MACHADO<sup>2</sup>**  
**Heinz KUTZNER<sup>3</sup>**  
**Ana AFONSO<sup>4</sup>**  
**Raquel VIEIRA<sup>1</sup>**  
**Fernando MALTEZ<sup>5</sup>**  
**Jorge CARDOSO<sup>1</sup>**

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## Tocilizumab-induced erythroderma

Tocilizumab is a humanized anti-human interleukin 6 receptor (IL-6R) antibody, engineered by grafting the complementarily determining regions of a mouse anti-human IL-6R antibody into human IgG1 to create a human antibody with a human IL-6R binding site [1, 2]. Tocilizumab binds to the IL-6 binding site of human IL-6R and competitively inhibits IL-6 signaling. A series of clinical studies have shown that inhibition of IL-6 signaling by tocilizumab is therapeutically effective in Castleman disease and rheumatoid arthritis (RA). In Japan, tocilizumab began to be widely used for patients with Castleman disease and RA refractory to other therapies in 2005 and 2008, respectively. We report a 62-year-old Japanese woman who developed erythroderma after administration of tocilizumab for her RA.

Twenty four years before our first examination, the patient was diagnosed as having RA because of multiple arthralgia. Although she took oral non-steroidal anti-inflammatory drugs (NSAID), oral corticosteroid and methotrexate, the arthralgia gradually worsened. She was referred to our hospital for further treatment of RA. The patient began to receive an intravenous injection of tocilizumab, 280 mg (8 mg/kg) once per month. Two days after the first injection, the patient noticed a slight erythematous eruption on her face, which subsided in a few days. One day after the second injection, she again developed erythema on the face to chest, although, it disappeared in a few days without any treatment. A few hours after the third injection of tocilizumab, generalized erythema developed on the whole body with severe itch (*figure 1*). There was no oral exanthema. A peripheral blood sample showed a normal leukocyte count of 4800/ $\mu$ L (Normal: 3500-9500) with 15.9% eosinophils (763/ $\mu$ L). The serum levels of hepatic enzymes were within normal ranges. She had neither a high fever nor lymph node swelling, suggesting that she did not suffer from viral infection. We could not obtain her informed consent for a skin biopsy. Since the eruption and eosinophilia occurred in accordance with the drug injection, we diagnosed her erythroderma as a skin eruption due to tocilizumab. Since we could not obtain her informed consent for further examinations, we did not perform skin patch testing or lymphocyte stimulation tests. The administration of tocilizumab was discontinued and the erythroderma subsided in a week with topical betamethasone butyrate propionate alone.

Tocilizumab inhibits the signaling of IL-6, an important inflammation moderator. Several kinds of serious adverse events due to tocilizumab have been reviewed by Nishimoto N *et al.* [3]. Infections such as pneumonia, herpes zoster, acute bronchitis and pyelonephritis are the most frequently observed side effects. However, aside from herpes zoster, only one case of cutaneous adverse effects of tocilizumab has been reported in the English literature [4].